GASTRIC ACID DEFICIENCY

PATHOPHYSIOLOGY AND CLINICAL EXPERIENCE

BY
V. VARRÓ

STUDIA MEDICA
SERIES
SZEGED

In memory of my Mother

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FOREWORD

Physiological and pathological problems of gastric acid secretion have been widely discussed in the literature for many years. Increased HCl production was mostly investigated, first of all in connection with ulcer disease and gastritis. For long the concept prevailed that superacidity not only necessarily accompanies ulcer disease and acute gastritis but represents one of the most important pathogenetic factors as well. In recent times superacidity is not held to represent a decisive pathogenetic factor in these diseases, moreover, the diagnostical significance of qualitative and quantitative changes of gastric acid secretion are questioned owing to the great variability of acidity in the same person.

Our knowledge is much more limited concerning the diminished secretory activity of the gastric glandular cells. As to the clinical significance of anacidity the views generally accepted are rarely based on well established clinical investigations.

In the present work we publish our experience and investigations concerning the pathophysiological and clinical consequences of the secretory deficiency of gastric glands. Based on experimental observations we try to follow the development of the secretory failure, to establish the proteolytic capacity of the anacid gastric juice and to clear up the interrelation between gastric dye excretion capacity and HCl secretion. Our clinical observations try to answer the questions whether definite signs and symptoms are caused by the lack of gastric acid, whether some pathological conditions — in the first place pernicious anaemia and funicular myelosis — are in causal relation to achlorhydrias and, how decreased secretory capacity of the stomach influences the bacterial growth in the upper part of the gastrointestinal tract. A critical analysis of all procedures, both experimental and diagnostical, which are used for the detection of achlorhydria, is presented.

The investigations published in this work were performed in the Ist Department of Medicine, Szeged University Medical School in the period between 1953 and 1960.

I wish to express my sincere thanks to those whose generous help made the appearence of this work possible. Above all I owe a great debt of gratitude to my former master, the late Professor G. HETÉNYI. It was his wise instructions and kind encouragements which directed me not only in writing this work but in every instance of my medical activity. His outstanding personality inspired me to devote myself to clinical and experimental gastroenterology, my first attempts in this field were helped by his useful advices and valuable suggestions.

I feel greatly indebted to my honoured chief, Professor Miklós JULESZ, Head of the I-st Department of Medicine, Szeged University Medical School, whose generous support made the accomplishment of my investigations possible.

To be able to investigate the problem of achlorhydry in detail I was obliged to ask the cooperation of specialists in all those examinations which were outside the field of internal medicine. Thus the investigations described in the chapter dealing with bacteriology are the result of a common work with V. BALÁZS M. D., Chief of the Bacteriological Laboratory of the Clinic with the cooperation of I. CSERHÁTI M. D. and F. SZARVAS M. D. The same is true for the neuro-psychological investigations which were performed by M. VARGHA M. D., Lecturer in the Department of Neuro-Psychiatry. To all of them I feel greatly indebted; without their generous cooperation these two chapters could never have been written. F. SZÉCHENYI M. D. collected some normal answers to the questionnaire test used in the psychological examinations; I hereby thank him for his help.

In the last phase of my work my dear friend and coworker F. SZARVAS M. D. assisted in the investigations and in the collection of materials; I wish to express my warm thanks to him. L. CSERNAY M. D. offered generous help by performing some of the enzyme determinations; to him my gratitude is due.

My thanks are also due to Mrs I. MIKLÓS for valuable technical assistance.

To my wife I wish to express my appreciation for her understanding attitude towards my research and for her most active help in the preparation of the manuscript for publication. Thanks are due to E. KELEMEN M. D. for his valuable suggestions while revising the translation of the manuscript.

Finally I wish to express my sincere gratitude to all my colleagues, the staff of the I-st Dept. of Medicine for generously admitting to perform the necessary examinations on their achlorhydric patients.

Szeged, August 1962.

V. V.

SECTION I.

Introduction

I. TERMS FOR THE VARIOUS TYPES OF GASTRIC SECRETORY INSUFFICIENCY

In the literature various expressions may be found to define various degrees of the failing gastric secretory function. It seems useful to revise them for *they do not always cover the same ideas.*

The term *„achylia gastrica"* was apparently first used by EINHORN (1892); it meant for him an absence of both gastric acid and enzyme. Etymologically achylia gastrica means total absence of gastric juice, that is a state in which no gastric secretion whatsoever occurs. This phenomenon is extremely rare, but may sometimes be encountered. KATSCH (1953) called it *„dry achylia"* and thought it to be the most grave form of anacidity. Some use the term *„pernicious achylia"* to separate the anacidity of the Addison-Biermer anaemia; this achylia is mostly a dry one. As one can find some mucus secretion in all gastric contents, practically achylia does not mean anything else but *lack of acidity and enzyme activity.* In the following we shall use the word in that sense and denote with *„absolute (dry) achylia"* those cases where no gastric juice could be detected at all. *„Apepsia"* or *„afermentia"* are two terms for an isolated lack of pepsin. These terms have no practical value at all as one cannot find acid gastric juice without enzyme content. *„Anadenia"* is the word recommended by EWALD for the total lack of gastric glands and gastric secretion consecutively. The same process i. e. the disappearence of the gastric mucosa is reflected in the words *„gastric cirrhosis"* or *„gastric phthisis"*. The last three terms are rarely, if ever, encountered in the modern literature.

For an absence of gastric hydrochloric acid the words *„anacidity"* or *„achlorhydry"* are generally and interchangeably used. Formerly it was the first, recently the second which prevailed in medical articles. Strictly taken *anacidity means the lack of both free and total acidity* (i. e. a gastric juice not containing titrable acid up to the change in colour of phenolphthalein), but one seldom finds it used in that sense. We think the term *achlorhydry* the most suitable to express *lack of free hydrochloric acid* in the gastric juice (a juice which does not turn the Congo paper to blue). When writing about our own experiments, we shall use the word achlorhydry for absence of hydrochloric acid, otherwise it will be interchangeably employed with the term *anacidity.*

It may cause some misunderstanding that various authors use various methods to assess the lack of acid in the gastric juice. Naturally the achlorhydry found after simply emptying the stomach or after a bread and tea test meal means less than the same finding after giving parenteral histamine and having simultaneously aspirated the secretion for 90 minutes. That is why the expression of *achlorhydria spuria* (pseudoachylia) is used by some authors for results achieved by procedures inadequate

to prove the real inability of the gastric mucosa to secrete hydrochloric acid. *This restriction seems essential to the proper evaluation of literary data.*

It can be frequently encountered in the literature — one may say that before the histamine era it was almost general – that the achylia was established entirely on the base of a simple emptying of the stomach or of a test meal using caffeine as the only stimulant. Consequently literary data from before the histamine era cannot be used for the proper estimation of the incidence of achlorhydry. Later in this monograph we shall always try to inform the reader about the criteria on which the diagnosis of achlorhydry was established in a certain material; this is, however, frequently impossible because of incomplete data regarding the gastric function tests used.

The term *„true achlorhydry"* is generally used for lack of hydrochloric acid after histamine administration. This term – although most useful clinically — is vulnerable theoretically as augmented doses of histamine may result in HCl production even in some of these cases.

Experiments with the dye neutral red forced us to revise once more the definition of achlorhydry. Some authors have expressed the opinion that a real criterion of achlorhydry would be the negative result of the chromoscopic investigation. Others have published cases where free HCl could not be demonstrated after giving parenteral histamine and neutral red simultaneously, but judging by colour changes the dye made its appearence in the gastric juice. We shall try to prove in the chapter dealing with the excretion of neutral red that these cases belong properly among the pseudo-achlorhydric ones. One may suppose namely with great possibility that a minimal amount of HCl was produced even in these patients which owing to subsequent neutralisation could not be demonstrated with the titration technique.

While employing modern methods, some of the terms used in the past for achorhydry have become meaningless and therefore can be omitted.

The following terms will be used throughout this monograph:

absolute (dry) *achylia:* a total lack of gastric juice,

achylia: lack of HCl and enzymatic activity,

achlorhydry (anacidity): lack of free HCl,

histamine refractory achlorhydry (anacidity): absence of HCl production after the usual dose (0,5—1,0 mg) of histamine,

true achlorhydry: lack of HCl and neutral red secretion after an augmented dose of histamine.

The difference between the terms histamine refractory achlorhydry and true achlorhydry is merely quantitative and by no means qualitative. Even in cases of true achlorhydry after giving large doses of histamine minimal production of HCl may be preserved which cannot be demonstrated by the conventional titration method. There is no proof whatsoever that the doses used in the augmented histamine test (3—4 mg of histamine) would represent the maximum of stimulus for the acid producing mechanism of the gastric mucosa.

II. CRITICAL ANALYSIS OF THE TEST MEALS USED FOR THE DETECTION OF ACHLORHYDRIA

Achlorhydry represents a state where the gastric mucosa is incapable to produce hydrochloric acid. The gastric secretion depends, however, not exclusively on the secretory capacity of the gastric mucosa but also, for a great part, on the quality and intensity of the stimulus. It is extremely important, therefore, to know what sort of gastric function test was employed when the diagnosis of achlorhydry is mentioned.

The procedures for investigating gastric secretion are generally called test meals because the first wide-spread method of gastric analysis, that of EWALD and BOAS (1886) was a real meal with bread and tea. Results achieved in the period of 1910 to 1924 were mostly based on this method. The EWALD—BOAS method was soon followed by other test meals which contained various kinds of food representing more potent secretory stimuli than bread and tea, as the test lunch of RIEGEL (1908), the test meal of CURSCHMANN (1910), the oatmeal soup of CROHN and REISS (1921), the test meal of SALAMANCA (1930) etc. These procedures have the common advantage that they use food, the most natural secretory stimulus; their common disadvantage is, however, that food and its constituents (proteins, products of proteolytic activity, organic acids, phosphates etc) influenced the point of change of colour of the indicators and had buffering property. That is why a test meal with simple water (tap or distilled) was recommended by BERGEIM et al. (1914). An important step forward was achieved by the introduction of caffeine solution for secretory studies by KATSCH and KALK (1923). This method (or its counterpart used in the Anglo-Saxon countries where alcohol is mostly employed instead of caffeine) created favorable conditions for the titration, but the question remained open whether or not the caffeine or alcohol represents a stimulus sufficiently strong for the HCl production.

Nowadays the most popular stimulant for secretory studies is the histamine. If HCl cannot be detected in the gastric juice withdrawn fractionally or continuously during 90 minutes after giving a patient histamine base* in a dose of 0,1 mg pro 10 kg body weight, the result is interpreted (the definition is derived from Bergmann) as *histamine refractory achlorhydry*. One may frequently encounter that this term is interpreted clinically as something definitive i. e. the ability of the stomach to produce HCl is thought to be lost absolutely and irrevocably.

* The proportional molecular weights of histamine base, histamine dichloride and histamine diphosphate are 111 : 184 : 307 respectively (SEIDMAN and NECHELES 1935); various pharmaceutical preparations do not contain, therefore, the same quantity of histamine in 1 mg of substance. The histamine quantities mentioned throughout this work refer always to histamine dichloride.

There exists convincing evidence that histamine is the most potent secretory stimulant for HCl we actually possess, for the everyday medical practice, therefore, this assumption may be acceptable. But for scientific reasons one must rely upon the fact that according to various authors and to data exposed later in this work, a considerable part of the so-called histamine refractory achlorhydric patients did not loose their ability to produce HCl. It seems reasonable, therefore, to ascribe to achlorhydry a mere quantitative meaning instead of a qualitative one.

A considerable proof of this assumption is given by the augmented histamine test (CONARD et al. 1949, KAY 1953, CARD et al. 1955, MERTEN 1959, CALLENDER et al. 1960). This procedure is based on the fact that antihistaminics protect the organism against undesirable side effects of histamine without influencing its stimulative action on the parietal cells. Consequently under „antihistamine-umbrella" histamine in much larger doses than usual (3—4 mg) may be injected which exerts an increased stimulation on the acid producing structures of the gastric glands.

The gastric analysis after insulin induced hypoglycaemia (sometimes mentioned as Hollander's test) did not gain general acceptance as a routine method. It was used for a while to control the perfectness of vagotomy but at present vagotomy itself has become an exceptionally rare operative procedure, on the other hand the theoretical basis of the insulin test does not seem to be indisputable according to the objections of HUNT (1949). The unpleasant and incalculable side effects of the hypoglycaemic reaction represent the major disadvantage of the insulin test. As an advantage one may mention that mainly through vagal excitation the acid, enzyme and mucin production are equally stimulated by the hypoglycaemia. The stimulation of the acid producing cells should happen (GLASS and WOLFF 1950) exclusively through liberation of gastrin; according to our investigations (VARRÓ et al. 1952), however, a double chain of events exists: simultaneously with the liberation of gastrin there is a direct way of vagus-acetylcholine-HCl as well.

The gastric juices obtained in test meals are further examined after filtration. Insoluble mucous substances, mucosal debris and cellular material are removed through filtration, but not the soluble mucin. While determining the degree of acidity, one must bear in mind that the titration does not take place with a pure HCl solution but with a biological juice containing HCl as well. The organic and inorganic constituents of the gastric juice exert a certain influence on the process and result of the titration, which should not be left out of consideration at the interpretation of the results.

For the proper estimation of the values of „free acid" one must also consider that proteins of amphoter nature have alkaline characteristics in the acid gastric content and thus are able to bind acid. During the titration while giving caustic soda to the gastric juice parallelly with the process of neutralization, H-ions are liberated from the protein-acid binding. It is not the „actual acidity" i. e. the acidity which is present at the beginning of the titration that is determined with the titration, but the „potential acidity" i. e. an acidity which arises from the changed dissociation of H-ions caused by adding alkali to the solution.

This source of error may be quite considerable in the case of protein containing stimulants (e. g. test lunch); with stimulants without protein content (caffeine, histamine) it can be neglected. Proteins eventually present in the gastric juice (blood, mucin, pus, exudate) are naturally of the same importance.

Total acidity represents the sum of acidic valencies i. e. besides HCl also CO_2, lactic acid and acid phosphates. In gastric juices containing sufficient HCl but no

proteins, the free and total acidity increase parallelly; a significant divergence suggests the presence of proteins, moreover in subacid juices lactic acid and carbon dioxyde.

On the basis of the theoretical objections raised against the value of the titration method some recommended its replacement by the determination of the pH of the gastric juice. The measurement of the pH is based on the registration of dissociated H-ions and thus reflects actual acidity indeed. Unfortunately it needs special adjustement, is not free from technical errors (ROVELSTAD et al. 1952), and cannot be properly used in case of superacidity. Generally it is difficult to registrate values inferior to pH 1,1 a point which corresponds to 86 clinical degrees of acidity; all possible acidity values above this — according to the appropriate remark of KALK an KUGELMANN (1925) — „disappear in the tiny difference between pH 1,0 and 1,1".

Although in everyday practice the registration of gastric pH could not replace the titration, its importance has increased lately mainly through results achieved by intragastric pH measurement. Continuous pH recordings made with modern technical adjustements give valuable information about pH changes during eating and after administering various drugs. (HOFSTÄTTER 1947, KREITNER et al. 1949, KINZLMEIER et al. 1951.)

An easy and comfortable method was worked out by SEGAL et al. (1950) for the semi-quantitative determination of gastric acidity. With cation exchange quinine resin it is possible to ascertain whether at the time of the investigation dissociated H-ions are present in the gastric juice.

H-ions eventually present in the gastric juice replace namely the cation part of the ion exchange medium and the free cation (in this case the quinine) absorbed from the intestine is excreted into the urine. Quinin determinations are made in the

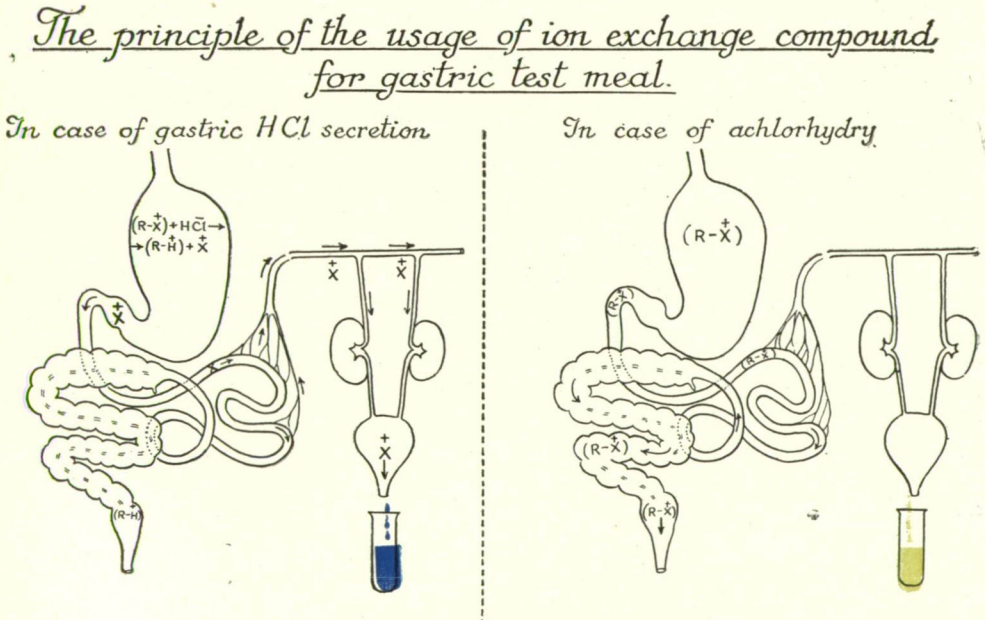


Figure 1

urine. In achlorhydrics the quinine cation remains bound and so no quinine can be demonstrated in the urine.

Lately the difficulties of the quinine determinations are abolished by combining the resin with a dye (azure A). In case of HCl production the change of colour of the urine indicates the presence of acid. In achlorhydric patients the colour of the urine remains unchanged (SEGAL et al. 1955).

In Europe instead of using cation exchange compound a preparation called Gastrotest (CILAG) is widely employed. Gastrotest contains a dye, pyridacyl (3-phenyl-azo-2,6, diaminopyridin) bound to protein; its solubility is minimal at pH above 3,0 but increases rapidly beneath it. Thus in the presence of HCl depending on the degree of acidity more or less dye becomes solved in the stomach and reaches after intestinal absorption the kidneys, resp. the urine. In case of achlorhydry only a minimal amount of the dye may find its way into the urine.

Several authors published reports on experience with Gastrotest (BIANCHETTI and GERBER 1958, ZSEBŐK and EGEDY 1959, MERTEN 1959, GARAI 1959, BALASSA 1960, ZALAY et al. 1960, HAMMERL and HOLLER 1961).

Our own experience is based on 60 investigations. In 47 of them the results achieved with Gastrotest could be compared with the acidity values obtained by an ordinary gastric analysis. In the remaining 13 cases this could not be done because the aspirating tube could not be introduced.

Our impressions could be summarized as follows:

1. There is no strict parallelism between the results of the test meal and those of the tubeless method. As considerable variations may exist in the results of test meals made on consecutive days, it is not excluded that the results achieved by the Gastrotest reflected the real acidity at the given moment.
2. In some cases during a test meal HCl was detected in patients qualified as achlorhydric by the Gastrotest procedure.
3. In 32 patients found achlorhydric by the routine gastric aspiration, the presence of HCl was indicated by the Gastrotest in 4 cases. In all of them repeated aspirations in our laboratory verified the preservation of HCl secretion. In the other 28 patients neither the ordinary test meal nor the Gastrotest could demonstrate any acid. It may be important to know that in no single case found „true achlorhydric" with the augmented histamine test, did the Gastrotest show any sign of HCl production.

To summarize our opinion we may say that Gastrotest seems to supply valuable semiquantitative information about gastric acidity. The appearence of a certain quantity of the dye in the urine indicates with great probability the presence of HCl in the stomach. For the detection of achlorhydry the Gastrotest may only be used as a screening test, for patients with scanty acid secretion may be qualified achlorhydric with this method. It seems appropriate, therefore, in patients found achlorhydric with the simple Gastrotest method to repeat the investigation after giving histamine or to perform a normal gastric aspiration after histamine injection.

III. METHODS AND MATERIAL

Aspiration of gastric juice

To assure a nearly complete evacuation of the gastric juice produced in a given period is a hitherto unsolved problem. The results are altered by the loss of gastric juice through the pylorus and by the admixture of the intestinal contents (bile, pancreatic and duodenal juice). The position of the tube may represent another source of error, because after curling its head may take a position from where no juice can be aspirated. The contamination of the saliva may also influence the result both qualitatively and quantitatively. Finally, withdrawing fractionally the gastric contents with a syringe does not result in total emptying of the stomach.

To inhibit the regurgitation of the duodenal contents aspirating tubes with double lumens were prepared. In one type a balloon was attached to the tube and placed in the pylorus or immediately beneath it; the balloon inflated hindered the regurgitation of the intestinal contents. In the other type the lower part of the tube was placed in the duodenum, the upper one in the stomach. By exerting simultaneous suction on both lumens, the duodenal contents too could be removed.

These tubes have more theoretical than practical value. The mere passage of the tube through the pylorus causes the investigation to become more difficult and to last longer. The position of the tube — even if controlled at the beginning of the aspiration — does not remain constant, because the lower part of it is pushed forward by the peristalsis (expecially the tubes with the balloon in the pylorus).

In our investigation the balloon was placed exactly beneath the pylorus, the upper part at the bottom of the stomach. The end of the tube was fixed to the mouth; in spite of this, controlling the situation radiologically about an hour later, the balloon was found 10—15 cm lower in the duodenum and the aspirating holes beneath the pylorus. As the other end of the tube remained fixed, this could be explained only by presuming the contraction of the stomach, which indeed seemed to be contracted in the X-ray picture.

To create optimal conditions for the aspiration the following method was adapted; we let the tube to be swallowed and then controlled the exact position of the head-piece with X-ray. The oliva has to lie at the bottom of the fundus with no curling of the tube. The other end of the tube was fixed to the mouth. The patient took a recumbent position on his left side. In this position namely the gastric juice is collected in a little pool (the „Schleimteich" of the German authors) and can be aspirated therefrom easily.

The contamination of the saliva was eliminated by the use of a dental-type continuous suction apparatus. The collection of the gastric juice was achieved with continuous aspiration too. The apparatus used was constructed after the model of

HOLLER (1951). In control studies we could ascertain that nearly all of the fluid injected into the stomach could be recovered by this method, while—according to KAY (1953) — with fractionally withdrawn gastric contents a loss of approximately two third of the secretion produced could be expected through the pylorus. To eliminate the psychic effect of the rumbling, the motor pump was placed in the adjacent room.

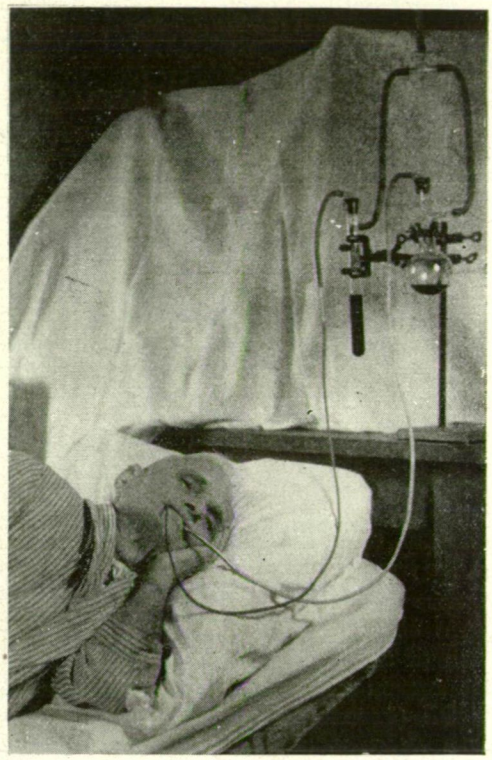


Figure 2.
Position of the patient during the histamine test meal.

Duodenal regurgitation is not entirely abolished by the left side position but only diminished: the investigation is carried out, however, under more natural conditions, than with the balloon technique. We want to emphasize the importance of the radiological control of the position of the tube and that of the continuous aspiration for detecting pseudo-achlorhydria. A separate group will be formed from patients thought achlorhydrics by the conventional aspiration technique in which with the method described above more or less acid production could be verified.

Administration of neutral red

Neutral red was injected in a 1% solution (5 ml) intramuscularly. The time elapsed between the injection and the appearence of the dye was registered. In case

of bile regurgitation the colour of the neutral red present in the bile (gold yellow) could be easily distinguished from the purple red colour of the acid gastric juice containing the dye. If there was doubt about the origin of the red colour of the gastric contents, extraction with amylic alcohol (JÁVOR 1956) was performed.

1 ml of gastric juice containing neutral red is neutralized with n/10 NaOH; i. e. titrated up to a golden yellow colour. Then it is diluted, depending on the colour intensity, with NaOH-borate buffer of pH 10 and 2 ml of the dilution are shaken with amyl alcohol. Nearly all of the dye passes over into the amyl alcohol but not bile, haemoglobin and other dyes in the serum. Separation of the alcoholic phase from the aqueous is achieved by vigorous centrifugation. The alkaline neutral red diluted in amyl alcohol is pale yellow.

Neutral red was injected simultaneously with histamine (but not in the same syringe!). Quantitative neutral red determinations were not made.

Dosage of histamine

Histamine (Peremin-CHINOIN, Histamin-RICHTER) was injected after collecting for 15 minutes the gastric content of fasting experimental persons. After injection the continuous suction was maintained for 90 minutes, emptying the collecting flasks in every 15 minutes. The augmented histamine test was performed as follows: an injection of an antihistamine preparation was given to the patient half an hour before the histamine administration. In case of 1-2 mg of histamine 50 mg of Pyribenzamin, 100 mg of Antistin, 20 mg of Synopen or 25 mg of Sandosten resp. were administered, in case of 3-4 mg of histamine the dose of the antihistamine was doubled. The pre-treatment with antihistamine does not influence the stimulation of the HCl production by the histamine, but saves the patient from the systemic side effects.

The patients tolerated the high doses of histamine excellently; even those complaints which generally could be observed after 0,5 mg of histamine (headache, feeling of warmth etc) were absent in most cases.

We want to call attention to the fact that flushes characteristic of histamine made their appearance throughout the body without any subjective complaints. The ineffectiveness of antihistaminics against the flushes caused by histamine was already demonstrated in our previous communication dealing with intraarterial histamine administration (OLÁH, VARRÓ and HETÉNYI 1955).

It is interesting that during the augmented histamine test systemic side effects — if present at all — were more intensive with smaller doses of histamine. Even the secretory reaction was not always the most intensive after the maximal histamine dose used; this our experience completely agrees with that of DOMINICI and FURBETTA (1953).

For the qualitative demonstration of the presence of HCl Congo paper, in case of a minimal quantity of gastric juice Günzburg reagent was used. With the Günzburg reagent it is possible to prove the presence of HCl even in a concentration of 0,01 per cent (cf. BÁLINT 1952). The blue colour of the Congo paper signifies pH values beneath 3,0, the turning to dirty-red of the indicator means pH values between 3,0 to 4,0. All collections were titrated against n/10 caustic soda using 0,5 per cent dimethylaminoazobenzene and phenolphthalein solutions as indicators.

Peptic activity was determined with the modified method of ANSON and MIRSKY (1932). For details of the method we refer to our earlier communications

(VARRÓ et al. 1951, FAREDIN et al. 1954). Cathepsin and trypsin determinations were performed on the base of haemoglobin digestion according to the method of MERTEN (1950).

The principle of all three procedures is that a solution of denaturated haemoglobin is incubated with the gastric juice, the protein which is not digested is removed with trichloracetic acid and the quantity of tyrosine liberated is determined photometrically. The digestion occurs at pH values of 1,5 for pepsin, 3,5 for cathepsin and 7,5 for trypsin. By this procedure the optimal (potential) proteolytic activity is determined for all three enzymes by creating an artificially optimal milieu for the enzymatic activity. The effect of inhibitors is blocked by using proper dilutions of the gastric juices.

In case of peptic, catheptic or tryptic activity, resp., values are expressed in tyrosine mg per ml gastric juice. Limits of reproducibility are presented in Table 2.

Table 1.

Quantitative data of the inhibition of peptic activity in gastric juices of various dilutions

No	Diagnosis	Gastric juice					
		Undiluted	1/25 dilution	1/50 dilution	1/100 dilution	1/150 dilution	1/200 dilution
		Peptic activity mg tyrosine/ml gastric juice					
1.	Sine morbo	3	13	14	14	14	17
2.	Sine morbo	3	20	18	17	16	19
3.	Sine morbo	3	14	16	11	17	15
4.	Sine morbo	4	37	42	41	41	41
5.	Duodenal ulcer	4	34	32	32	32	33
6.	Duodenal ulcer	6	52	61	60	62	59
7	Duodenal ulcer	5	44	48	47	48	47
8.	Duodenal ulcer	5	41	46	44	44	44

Taking sample for the bacteriological investigations

A sterile doudenal tube is passed into the patient holding it with hands in sterile rubber glove paying attention that the olive should not touch but the pharynx at swallowing. To control possible contamination which may happen in the pharynx the flora of the pharynx was determined before every investigation. If the bacterial

Table 2.

Limits of reproducibility of gastric enzymatic activity.

Peptic (catheptic, tryptic) activity in mg tyrosine/ml.

Degree of dilution	No enzymatic activity	Enzymatic activity in traces	Poor enzymatic activity	Sufficient enzymatic activity
50 x	< 1,6 mg	< 2,3 mg	up to 20 mg	more than 20 mg
100 x	< 3,2 mg	< 5,0 mg		
200 x	< 6,4 mg	< 10,0 mg		

population of the gastric juice and the pharynx were identical, the result was presented as „pharyngeal flora". After aspirating the fasting gastric content for 15 minutes the posthistaminic gastric juice was used for the bacteriological investigation. The bacteria were cultured within 2 to 3 hours after the aspiration of the juice. The sterility of the duodenal tubes was controlled several times and the results were reassuring. The swallowing of the saliva was inhibited by the suction apparatus.

Culture and identificiation of the bacteria

In the time elapsed between the aspiration of the juice and the inoculation the material was kept in an icebox. Then the gastric juice or the duodenal content was centrifuged and the sediment inoculated into blood-agar or endo media. They were incubated in thermostats at 37 °C for 18-24 hours. Isolated colonies were stained by Gram's method. Gram negative and positive cocci are uniformly called in this work as „pharyngeal flora". The following biochemical properties of the Gram negative bacilli were determined: splitting of dextrose, lactose, saccharose, maltose, mannit and sorbose; production of H_2S; urease activity; indol formation; methyl red and Voges-Proskauer reaction. The denotation of bact. coli is used in the following for members of the coli-aerogenes group.

Method for estimating the number of living bacteria

Enumeration of the living bacteria was made by the modified dilution technique of Balázs and Cserháti (1959). The number of bacteria was established on the basis of two parallel counts.

Gastroscopy

Gastroscopy was performed with the Wolf-Schindler flexible instrument after anaesthetisation with 1 per cent pantocaine solution containing epinephrine.

Material

Investigations were carried out on patients of the I-st Department of Medicine of the University Medical School of Szeged, who were found achlorhydric at the station after a routine gastric analysis with 0,5 mg of histamine. A few patients came from the Department of Neurology, where they were treated for symptoms of funicular myelosis.

SECTION II.

Experimental studies

IV. INVESTIGATION OF HYDROCHLORIC ACID PRODUCTION

Anatomical considerations

The gastric mucosa contains the whole secretory apparatus of the stomach. The organs of secretion are the glands, which, embedded in soft connective tissue, line the inner surface of the stomach. The mucosa is separated from the submucosa by a smooth muscle bunch having 2 or 3 layers, called the muscularis mucosae. The mucous membrane forms numerous folds between which the gastric crypts (foveolae gastricae) are situated. Into each crypt on the average 4,3 gastric tubules are opened in the adult, which means an average number of about 14 millions of gastric glands.

The glands are covered by a line of columnar epithelium (surface epithal cells) which forms the innermost layer of the stomach. They are ubiquitous constituents of the mucosa and produce mucous material. The short narrow entrance of the gland was named by ZIMMERMANN (1925) the isthmus; the next part the neck, and the bottom part of the gland, the body (corpus). In the neck of the tubule special mucoid cells (synonymes: chief cells of the neck, mucous cells of the neck, Nebenzellen) and parietal (oxyntic) cells can be found. The body of the tubule is formed mostly by the chief (peptic) cells, besides some parietal cells and occasional mucous cells can be detected.

The functions of these glandular elements and the diagnostical approach to control their function are demonstrated by Figure 3.

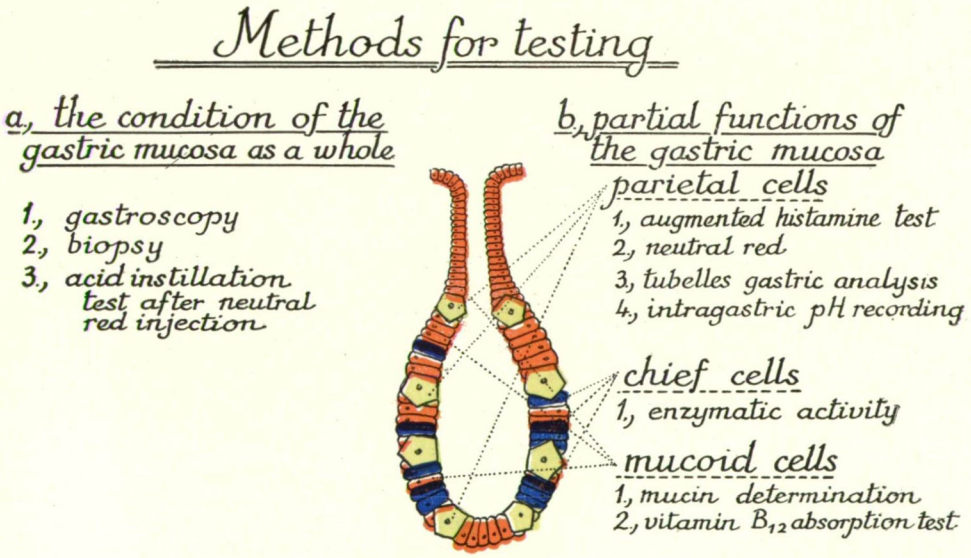


Figure 3.

The cellular composition of the glands is different in the various parts of the human stomach. A differentiation can be made, therefore, between cardiac, pyloric and fundus (chief) glands.

In man the zone of the cardiac glands is not extensive. Taking in account the individual variations its length does not extend more than 0,5 to maximally 4 cm caudal from the oesophageal mucosa. The mucous membrane is thin, the prevalent secretory cells are of the mucous type, here and there some parietal cells, occasionally a few chief cells are to be found. According to BENSLEY (1902) the cardiac glands are „decadent or retrogressive structures derived from the fundus glands by the disappearance of their more highly specialized cells".

An area of 4 to 5 cm proximal to the pylorus is occupied by the pyloric glands. The cells of the pyloric glands produce mucus and resemble the cells of the cardiac glands and the mucoid cells of the neck. There is no HCl production, as the presence of parietal cells are rather exceptional. The views are divergent as to the pepsin secretion of these glands. BABKIN (1928) has found proteolytic activity in the juice of the pyloric glands. HOLTER and LINDENSTROM-LANG (1935) are of the same opinion. IVY and OYAMA (1921), however, deny such a possibility. Anyhow the production of pepsin must be considerably less than in the fundus or in the corpus. The pyloric juice is alkaline, its pH ranging between 7,0 and 8,0 in the dog. The pyloric part does not play an essential part in the gastric digestion, but has an important function, i. e., the production of gastrin.

The corpus (fundus) glands occupy the whole of the gastric mucosa exclusive of the two areas mentioned. The mucoid cells of the neck produce mucin and urease. It can be maintained with great probability that during life the transformation of the mucoid cells into chief cells may take place. Under certain pathological conditions a reverse process may also occur; such a transformation has been observed in gastritis, gastric ulcer and gastric cancer; the whole gastric tubule contained only mucoid elements (KONJETZNY 1928).

Approximately two-thirds of the corpus glands are formed by the chief cells. It is commonly accepted that the chief cells contain the zymogen granules which are precursors of the enzyme (pepsinogen).

As it is supposed that not only precursor of the pepsin but also that of the catheptic part of the gastric proteolytic enzyme complex is formed in the chief cells, it seems better to use this notation instead of „peptic cells". The pepsinogen (cathepsinogen) secretion is only in part directed towards the lumen of the stomach, another part of it reaches the blood stream and is excreted into the urine (uropepsinogen, urocathepsinogen).

Parietal cells can be found mostly in the neck, less in the body of the glands. They are organs of the gastric hydrochloric acid production. In the body of the glands they are separated from the lumen by the chief cells; special intercellular capillaries make, therefore, possible that the secretion of the parietal cells should reach the lumen of the tubule. This process has an importance from the point of view of both of the HCl production and of the activation of pepsinogen.

The process of the hydrochloric acid production

Under normal conditions the cells of the gastric mucous membrane possess the ability to form from the almost neutral fluid surrounding them a strongly acid secretion. To express it more precisely, they are able to concentrate H ions a millionfold creating from the nutrient fluid of pH 7 hydrochloric acid with a pH value about 1.

The literature did not reach a definitive standpoint as to the site and manner of the HCl production. As early as 1858 CLAUDE BERNARD injected potassium ferrocyanide and ferrous hydroxyde into an animal, killed it and examined its stomach. These compounds give in the presence of free hydrochloric acid the characteristic Prussian blue reaction. From the fact that the inner surface of the stomach became blue but not the interior of the glands and of the cells, he concluded that HCl is formed bound to some material in the glandular cells and is set free only in the lumen of the stomach. This observation formed the basis of the experiments of HARVEY and BENSLEY (1912) and HOERR (1936). Using indicator dyes (neutral red, cyanamin bichloride) they concluded that the parietal cells secrete a protein hydrochloride, which undergoes hydrolysis in the gastric crypts with liberation of free HCl. The same speculation reappearing in a new form can be detected in the works of ZIMMERMANN (1925). According to him the parietal cells are capable only to produce an acid-precursor (acidogen), which is dissolved by the action of an enzyme (acidase) and so HCl is liberated.

In opposition to these views DAWSON and IVY (1926) maintain that the presence of HCl can already be demonstrated in the parietal cells if supravital staining is performed in due time. Using the mucosa of a secreting PAVLOV pouch they could observe a crimson color in the parietal cells (the acid color of the dye). A few minutes later after the cessation of the HCl production the cytoplasm and the canaliculi of the parietal cells presented a yellow color, indicating an alkaline reaction.

HOLLANDER (1943) reached the conclusion that acid is formed through membrane hydrolysis in the wall of the intracellular canaliculi. The wall of the canaliculi is – he maintains – irreciprocally permeable to water and to Cl ion (and to other halides) and so the hydrolysis of NaCl would happen as follows:

$$NaCl + H_2O \rightarrow HCl + NaOH$$

The HCl would be situated extra-, the NaOH intracanalicularly. The NaOH left after the hydrolysis would be neutralized by intracellular buffers and transferred into the tissue fluid in the form of $NaHCO_3$ or alkaline phosphate.

This theory corresponds fairly well with the earlier concept of MALY (1877-78) who described the starting-point of intracellular HCl formation in the transformation of acid phosphates to alkaline phosphates according to the formula:

$$NaH_2PO_4 + NaCl = HCl + Na_2HPO_4$$

In the blood alkaline phosphates are retransformed to acid phosphates and thus sufficient quantity of acid phosphates are available for further HCl production:

$$Na_2HPO_4 + H_2CO_3 = NaH_2PO_4 + NaHCO_3$$

This concept gives an explanation of the phosphate and carbonate abundance of the parietal cells in the intersecretory period and also of their scanty chloride content. During secretion there is an increase of the chloride content, of the parietal cells simultaneously with that of the bicarbonate level of the venous blood draining the gastric glands. New light is cast on the problem of the mechanism of gastric HCl production by the ingenious investigations of DAVENPORT and FISCHER (1940). Estab-

lishing the fact that the enzyme carbonic anhydrase is present in far greater amount in the gastric mucosa than in the other parts of the digestive tract, he set out the following theory: carbon dioxyde formed inside the parietal cells is quickly hydrated to carbonic acid by carbonic anhydrase. Subsequently carbonic acid is ionized giving hydrogen ions and bicarbonate ions. Hydrogen ions are concentrated and secreted as HCl, the bicarbonate passes into the blood in exchange for the chloride ions. In spite of the fact that Davenport's theory was repudiated by its author himself (DAVENPORT 1946) and other scientists (FELDBERG et al. 1940, HOVE et al. 1940) emphasizing that it is highly improbable that carbonic anhydrase should play a decisive role in the primary mechanism of HCl formation, with the advent of new, more potent carbonic anhydrase-inhibitors (e. g. 2-acetyl-amino-1,3,4 thiadiazole-5-sulfonamid) carbonic anhydrase is again estimated as an important factor in the intracellular synthesis of HCl (DAVIES 1948, JANOWITZ et al. 1952).

Interesting model experiments were performed by SZABÓ et al. (1951) to give an explanation of the gastric HCl formation. Taking into account the possibility that HCl can be formed from NaCl and from a weak acid with the aid of ion exchange resins, they considered the possibility whether a similar process could take place inside the body. To our knowledge no anion resp. cation exchangers have been yet demonstrated in the animal body, thus physiological importance of this finding is doubtful.

The theories mentioned above try to find an acceptable answer to the question of gastric acid formation but unfortunately, they cannot reach a definitive solution of the problem.

As to the intra- *versus* extracellular formation of HCl — considering the experimental data available — the intracellular, more precisely, extracanalicular appearence of HCl seems highly probable. The most convincing histochemical investigations of BRADFORD and DAVIES (1950) leave little doubt that at the time of gastric secretion a strongly acid milieu may arise in the pericanalicular zone, which cannot be explained otherwise but with the presence of intracellular HCl.

Negative results of earlier investigators were probably influenced by the following facts:

1. The parietal cells of the excised piece of mucosa were not secreting at the moment of the experiment. We have already mentioned that using neutral red it was established that a few moments were sufficient for the cessation of the HCl secretion.
2. Even at the time of HCl secretion the whole of the parietal cell mass is not secreting simultaneously. BRADFORD and DAVIES (1950) also demonstrated that gastric mucosa produces the acid in patches; areas with no activity alternate with secreting ones.

The problem of the intrinsic mechanism of HCl formation remains unsolved. There is no doubt, however, about the blood serum being the source of the Cl ions of the HCl formed. This assumption is supported by the fact that acid secretion stops in animals fed with diet containing no Cl ions and in animals fed with Br instead of Cl, hydrobromic acid is produced by the stomach. The well known physiological experience that the secretory capacity of the stomach is practically inexhaustible, strongly supports the idea that the source of HCl produced cannot be a metabolic product of the parietal cells but only the interstitial fluid respectively the blood plasma.

Regulation of the hydrochloric acid production

In man secretion of HCl is the result of a complex neurohumoral mechanism. Human gastric secretion is continuous opposite to the intermittent type of acid production of some animals (e. g. dog). There is gastric secretion even in the interdigestive periods which is essentially less, however, than that after eating. It remains an open question whether this capacity of continuous secretion indicates a spontaneous activity of the human gastric glands. The effect of stimuli namely other than food cannot be excluded in the interdigestive periods. Influence of conditioned reflexes may often be overlooked too. SOKOLOW (1904), BOLDYREFF (1907) and later KIM and IVY (1936) emphasized the secretion-stimulating effect of the saliva swallowed and of the duodenal juice regurgitated. On the other hand duodenal regurgitation may be demonstrated in the fasting gastric contents of man nearly in 100 per cent of the cases. (MEDES and WRIGHT 1928). The bilious coloring of the fasting gastric contents can be observed even with the naked eye in appr. half of the cases. It is well known that duodenal regurgitation into the empty stomach occurs regularly and the secretion of the fasting stomach is stimulated by this duodenal juice.

Food rest in the stomach or in the intestines, irritative effect of the duodenal tube, presence of gases in the stomach, all these contribute to the difficulty of determining the origin of the interdigestive secretion.

The quantity of the fasting gastric secretion is naturally significantly less than that of the secretory periods; according to REHFUSS and HAWK (1921) it is on the average 50 ml. After the removal of this juice a continuous secretion of a tiny quantity begins which does not, however, always contain HCl.

Soviet authors have called attention to the fact that the secretory process first starts in the glands of the lesser curvature. The function of this part of the stomach can be compared with that of the sino-auricular node in the heart (HETÉNYI 1954). The secretion of the lesser curvature not only starts earlier, but the juice secreted has a higher acidity and enzymatic content (DAVIDOV 1935, BYKOV 1935, 1941, KURZIN 1939). From a functional point of view it seems reasonable to differentiate a third secretory area in the stomach besides the fundic and pyloric ones, that of the lesser curvature (RIKKLY 1949).

The secretory mechanism in connection with eating can be divided into two main groups:

a) the cephalic (neural, psychic) phase

b) the chemical (gastric and intestinal) phase.

The mechanism of the *cephalic phase* has been elucidated by the classical experiments of PAVLOV. Accordingly reflexes stimulated by the food induce the action of the secretory apparatus through the vagus. The direct contact with the food is not absolutely necessary for afferent impulses to arise. The mere thinking of food or catching sight of palatable substances or things linked with eating initiate the reflex.

The secretion of the cephalic phase can be induced by the stimulation respectively blocked by the inhibition of whatever part of the reflex arch. Stimulation of central nervous structures (insulin hypoglycaemia) and vagal excitation result equally in typical vagus juice. On the other hand inhibition can be induced by blocking either the nervus vagus (atropine) or higher centres (narcosis). Thus we succeeded to diminish the cephalic secretion induced by insulin hypoglycaemia with sedatives or to block it entirely with narcosis. The hypoglycaemia itself was brought about, only its secretagogue effect disappeared (VARRÓ and OLÁH 1954). Also frontal leukotomy

diminishes the secretory response during insulin hypoglycaemia (VARGHA et al. 1951).

The cephalic (vagal) excitation seems to influence all sorts of secretory cells of the gastric glands, the products of parietal, chief and mucoid cells being equally represented in the juice produced. Experimental data support the hypothesis that vagus stimulation affects the chief cells and mucoid elements directly through acetylcholine liberation. Parietal cells, however, are not directly stimulated by acetylcholine, they need subsequent liberation of histamine (BABKIN 1950, BORBOLA et al. 1951) or gastrin (UVNÄS 1942, GLASS et al. 1950, VARRÓ et al. 1952) for the secretory process.

The first, gastric part of the *chemical phase* starts after food particles have come into contact with the gastric mucosa. The mechanism is a double one: partly the mucous membrane is mechanically irritated by the food, partly specific chemical influences are concerned. The former can be reproduced in model experiments inflating a balloon in the stomach (IVY and FARREL 1925, BYKOV 1935, KURZIN and SLUPSKY 1937). The effect of mechanical irritation is due to reflex activity; it disappears after vagotomy. On the other hand certain foodstuffs exert a direct specific action on the gastric mucosa liberating the secretory hormone, gastrin. The hormone is formed in the pyloric mucosa and reaches the glandular cells through the blood stream. TSCHUKITSCHEV (1930) succeeded in evoking secretion in fasting animals with the transfusion of blood taken from fed animals. GREGORY (1950-51) has proved that the histamine level of the blood transfused is not elevated which renders highly probable that the hormone liberated is not identical with histamine. Although gastrin can be produced in a sufficiently pure form (containing no histamine), the mechanism of its effect is not yet clarified (KOMAROV 1938, UVNÄS 1943). It has an action similar to histamine stimulating mainly acid production.

Food entering the intestine evokes gastric secretion a few hours later; this is called *the intestinal phase of gastric secretion* (second part of the chemical phase). The mechanism seems to be hormonal (SIRCUS 1953).

Giving ACTH and cortisone to patients it was observed that during treatment gastric secretion, especially that of pepsin, is increased (GRAY et al. 1951 a). There is also an increase of pepsinogen output in the urine (GRAY et al. 1951 b) and of the plasma pepsinogen levels (VARRÓ et al. 1956, 1960). Based on experiments PORTER et al. (1953) suppose the existence of an *adrenal phase* of gastric secretion. Electric stimulation of the posterior hypothalamus (the mamillary bodies and the tuber cinereum) evokes the secretion of HCl in monkeys. This secretion is not influenced by vagotomy or transsection of the spinal cord but is blocked by adrenalectomy. The authors suggest that a pituitary-adrenal secretory mechanism is mobilised by the hypothalamus.

The existence and importance of an adrenal phase in normal (physiological) gastric secretion needs further experimental proofs. The separation of the various secretory phases is an artificial condition which can be produced only in experiments. In reality during eating the various phases come into action together and side by side.

The regulation of primary (free) acidity

The fact that in various moments HCl of various concentrations can be found in the stomach has raised the question of the regulation of primary (free) acidity. The HCl is secreted by the parietal cells; this opinion is generally accepted, but there is much controversy as to the nature of HCl production.

The theories have two fundamental principles in common:

a) *Pavlov's conception of isochlorhydry.* PAVLOV (1910) maintains — on the ground of experiments in dogs with a gastric pouch — that the acid is secreted by the gastric glands in a concentration of constant strength and that variations in the acidity observed at the beginning and at the end of the secretion are caused by its partial neutralization by alkaline mucous substances.

b) According to Rosemann's conception (1907, 1920) acidity may undergo variations corresponding to the changing activity of parietal cells independently of the neutralizing effect of the alkaline mucus. The total chloride concentration of the juice is constant and it depends on the activity of the parietal cells how much Cl is coupled with the H ions to form HCl; the rest appears in the secretion as neutral chloride. This conception does not accept the term „superacidity" as concentrations of HCl in the gastric juice are limited by the total chloride content. Subacidity or anacidity arises when the greater part or even the whole of the chloride content is secreted in the form of neutral chloride but not of HCl.

Both conceptions acquired many adherents and opponents during the time elapsed. It is interesting to note that Pavlov's adherents are mostly physiologists, those of Rosemann mostly clinicians. This may be explained by the fact that physiological model experiments are very suitable to create conditions where isolated secretion of the parietal cells can be observed. On the other hand experiencing considerable acidity variations in everyday practice it is difficult for the clinician to get rid of the thought that these differences are not the consequences of a primary regulatory mechanism.

HOLLANDER's conception (1932, 1936, 1943) is based essentially on Pavlov's theory. The gastric juice is — according to him — the resultant of the work of various secretory cells. Parietal cells produce HCl having a concentration of about 170 m Eq. per liter, but no neutral chloride. The so-called „alkaline component" (a common designation for the non-parietal constituents) is isotonic with the blood; its cation concentration is also about 170 m Eq. per liter, which is combined partly with chloride (having a concentration of about 100 m Eq. per liter), partly with several buffer anions (their concentration being about 70 m Eq. per liter). The actual acidity is the result of the relative proportion of the two components.

ENGESTRÖM's conception (1935) contains details from both theories. He maintains that HCl formation is based on the principle of the isochlorhydry but „primary" regulation begins already in the tubuli with the reabsorption of H ions. The degree of the back diffusion of the H ions depends on the intensity of the secretory process. Acidity is further influenced in the stomach by „secondary" factors like duodenal regurgitation, mucus, diluting secretion etc.

Similar to Engeström's conception is the „diffusion theory" proposed by TEORELL (1933, 1935, 1939, 1940). According to him when primary acidity produced in the glands reaches the stomach HCl diffuses into the mucosa and thence into the blood. A continuous outward diffusion of HCl and simultaneous inward diffusion of NaCl (with a small admixture of HCl) takes place with a subsequent reduction of acidity. The velocity of the diffusion process is influenced by the concentration gradient of the H ion content of the gastric juice and the blood (resp. tissue fluids), by the thickness of the mucosa and the degree of its vascularisation and by the volume of the gastric secretion (the rate of diffusion being greater with a smaller volume on account of the relatively greater surface for the diffusion). We may mention that back-diffusion of HCl from the stomach was already verified by FAITELBERG in 1930.

Being an adherent to Rosemann's theory, KATSCH (1953) stands up for a physiological poikilochlorhydry. He interprets the fact that sometimes supersecretion with low acidity can be observed as an evidence for the primary HCl secretion of various concentrations. At the same time he emphasizes that the mucoid cells of the neck are able to produce a diluting secretion creating hereby the possibility of a secondary regulation of the HCl produced in a constant concentration.

Observations of physiologists and clinicians are unified in an eclectic manner in the conception of BABKIN (1931, 1934, 1938). He propounds the idea that the quality of the gastric juice is due to the unequal quantitative activity of the different groups of glandular cells. At least four groups of cells contribute their products to form the gastric juice, and the relative intensity of the secretory activity of these cell groups should determine the degree of acidity observed.

Reviewing the theories we are of the opinion that Pavlov's original conception of isochlorhydry — at least under normal conditions — may be accepted. Besides the HCl the most part of the water is secreted by the parietal cells again. The „non-parietal" elements produce their specific products (enzyme, mucin) and also a certain quantity of chloride and in all likelihood an alkaline (but at least neutral) diluting secretion

The relation of the acidic and alkaline products determines the degree of acidity. In all probability diffusion does not play a considerable role in the case of small amounts of gastric juice produced. Besides the above factors we must take into consideration the acidity-influencing property of the swallowed saliva, of the duodenal regurgitation and of the food particles.

Under pathological conditions the number of the influencing factors may be increased by specific effects arising from the given pathological events. Thus the elective destruction of the sensible parietal cells of great energy demand may represent a decisive factor in the regulation of acidity. The decrease of the „parietal cell mass" with simultaneous relative integrity of chief cells and mucoid elements may result in the development of clinical sub- or even anacidity. Considering this possibility LAMBLING and BERNIER (1959) distinguish between true and relative achlorhydry, the first representing the total absence of HCl production, the second the result of a neutralisation of the small amount of HCl by alkaline components. They attribute clinical importance to this differentiation.

Seldom a partial lesion of the parietal cells seems to develop; the production of HCl ceases but secretion of fluids continues. Such a case was published by KATSCH and KALK (1926 a, b). After acid poisoning they observed the reconstruction of the fluid-producing capacity of the parietal cells to precede HCl production of the same structures. In contrary elective stimulation of the parietal cells (e. g. with histamine) may reveal HCl secretion because simultaneously with the production of a minimal amount of HCl no secretion of the non-parietal (neutralizing) components occurs.

Histamine as the elective stimulant of hydrochloric acid secretion

Histamine seems to be at present the most effective stimulant of the gastric HCl production.

POPIELSKI (1920) was the first, to emphasize the gastric acid-stimulating effect of histamine. In further experiments it was elucidated that histamine acts mainly on the periphery; its effect may be demonstrable after vagotomy (KEETON et al. 1920, KOSKOWSKI 1922), in denervated (IVY and JAVOIS 1924—25) and, what is more, in transplanted gastric pouches (IVY and FARREL 1925). KLEIN (1932) succeded in

demonstrating that the secretion-promoting effect of histamine may be observed even if the transplanted gastric pouch is devoid of its muscular layers and myenteric plexus. Its effect is not abolished by atropine (KOSKOWSKI, 1922, LIM et al. 1923) although the intensity of the HCl secretion is diminished (POLLAND 1930, GRAY 1937).

Histamine seems to exert an elective effect on parietal cells (BABKIN 1930, GILLMAN and COWGILL 1931, BJÖRKMAN et al. 1943, ZAVODSKAIA 1953) without affecting the pepsin and mucus production. BABKIN even maintains that it inhibits pepsin secretion. BUCHER and IVY (1941) propound the idea that pepsin secretion is increased by histamine; their results, however, are not convincing in this respect. Very demonstrative experiments were performed by BOWIE and VINEBERG (1935). With special colouring they were able to prove that during histamine administration the quantity of the zymogen granules remains unchanged in the chief cells while vagal excitation led to total depletion of the same granules.

The exact mechanism of histamine effect is not yet clear. The dose which injected subcutaneously or intramuscularly results in an abundant secretion, does not stimulate the secretion of HCl when given all at once intravenously. Minimal amounts of histamine given in a slow intravenous drop infusion maintain a continuous secretory response. Maximal histamine response in dog either after a single s. c. injection or after i. v. infusion was found to be a linear function of the total number of parietal cells (MARKS et al. 1960). Endogenous histamine liberation which happens e. g. after rubbing the skin (KALK 1929) or at the time of the histamine headache (HORTON 1943) also evokes HCl secretion. The functional state of the glandular cells, too, exerts an influence on the secretory effect of histamine. TUMASS (1937) reported that the secretory response to histamine was enhanced after previous vagal excitation.

There are some data indicating that histamine has an indirect action on parietal cells (BORN and VANE 1953). If the histamine was allowed to mix with the blood for some minutes, the resultant secretion was greater than if injected directly into the artery of the stomach. The possibility of an indirect action is further supported by the ineffectiveness of antihistaminic preparations.

Occasionally one may find data reporting the secretion inhibitory effect of some antihistaminics. LEHMAN and STEFKO (1949) described that Thephorin (ROCHE) is able to inhibit the acid secretion evoked by histamine; NEUMAYR and SCHMID (1949) reported the same finding after longstanding administration of Antistin (CIBA). LUSSO (1950) observed some decrease of acidity after histamine in a patient pre-treated for a week with Neoantergan.

The great majority of the authors, however, are convinced that *antihistaminics have no inhibitory effect on histamine induced gastric acid secretion* (MOERSCH et al. 1946, GORDONOFF 1948, ASHFORD et al 1949, LINDE 1950, PATON and SCHACHTER 1951 etc).

The effect of histamine on gastric glandular structures may perhaps be influenced by the fact that the gastric mucosa does not contain histaminase, the histaminolytic enzyme (BEST and MCHENRY 1930). Contrary to the assertion of several authors (ATKINSON and IVY 1934, BIGURIA and CANZANELLI 1934, NECHELES and OLSON 1934, 1941) that the secretion of acid gastric juice could not be suppressed by histaminase, GROSSMAN and ROBERTSON (1948) succeeded to present a purified preparation of histaminase which not only inhibited the secretion evoked by histamine but also that stimulated by food and parasympathetic drugs.

In the human body parietal cells are the most sensible structures to histamine, this renders the investigation of the histamine effect very difficult. In dogs (non

anaesthetized) a dose of 0,04 μg/kg/min, in man that of 0,004 μg/kg/min is sufficient to evoke acid secretion (HANSON et al. 1948). At the same time the administration of 0,2-2 μg/kg/min of histamine is necessary for the registration of any changes in the blood histamine levels with the methods available at present (EMMELIN and KAHLSON 1944, IRVINE et al. 1961). The discrepancy between these two data indicates that the histamine sensibility of the parietal cells exceeds that of all other cells and thus we are not able to answer the question whether any changes in the plasma histamine level play an essential role in the physiological regulation of HCl secretion.

There is no doubt that presently histamine must be considered the most potent stimulant of the acid production and in our opinion after stimulation with sufficient quantity of histamine it is possible to detect HCl in all individuals whose gastric glands are still capable to produce acid. Histamine has the advantage not to stimulate the secretion of the „alkaline component" and thus even a minimal amount of parietal juice may remain unbuffered. The activity of the parietal cells cannot be exhausted by histamine. In SCHIFF's case (1938) a patient received 799 histamine injections during four and a half years without any signs of exhaustion or lesion of his HCl productive system. The effectiveness of the histamine test may be essentially raised by augmenting the doses of histamine. We shall try to demonstrate that with the aid of the augmented histamine test gastric acid production could be detected even in cases thought histamine refractory up to that time.

Besides histamine the insulin hypoglycaemia too is considered to be a potent stimulant of acid secretion. IHRE (1938) succeeded in demonstrating acid production after insulin hypoglycaemia even in a patient found achlorhydric after a dose of 1 mg of histamine. In Ihre's opinion histamine and insulin are equivalent stimulants of the HCl secretion.

For secretory studies, we held histamine superior to insulin. While insulin evokes the secretion of gastric acid, pepsin and mucin alike, histamine has the advantage of stimulating only the parietal cells. The insulin effect is rather incalculable with great individual variations which renders its use technically even more difficult. It is used partly for controlling the effectiveness of vagotomy (e. g. in denervated gastric pouches), partly for the experimental reproduction of the cephalic (vagal) phase of acid secretion. In the study of gastric acid secretion — especially of achlorhydry — preference must be given to histamine.

Our own observations concerning acid production

Investigations were carried out with continuous aspiration on 224 individuals who were found achlorhydric in our Clinic (a few in other institutes) after a routine test meal using 0,5—1,0 mg histamine.

In 45 of them HCl could be demonstrated even after 1 mg of histamine. In all likelihood it were the advantages of the aspiration technique and not the histamine dose which helped us to detect the acid.

The distribution of the acidity values in these cases were as follows:

in 4 individuals > 50 clinical units (i. e. 50 m Eq. per liter)
in 7 „ 20—50 „ „
in 18 „ < 20 „ „
in 16 „ only the presence of HCl was demonstrable, but quantitative acidity determinations could not be made.

Our results indicate that the majority of the patients examined were really subsecretors; in 31 out of 45 acidity did not reach 20 clinical units. The four patients

whose acidity was higher than 50 were evidently qualified achlorhydrics in consequence of a technical error.

So in one of them (F. J.) a big gastric *„poche d'air"* was demonstrable during X-ray examination in which the tube made manyfold curlings and could be forced into the correct position only with much trouble. In all probability at the time of the routine analysis the end of the tube was situated at the cardiac region from where no acid could be aspirated; from suitable points, however, a gastric juice of high acidity (55—66) could be gained.

In one hundred and thirty five patients among the one hundred and seventy nine in which no acid was demonstrable we performed test meals with augmented doses of histamine. Our results are shown in Table 3.

Table 3.

Gastric acid secretion in »anacid patients« (after a rutine test meal) following an augmented histamine test.

135 cases.

Dose of histamine	HCl production demonstrable	No HCl production
2 mg	39	14 *
3 mg	29	53

* A test meal with 3 mg of histamine could not be performed owing to technical difficulties.

Measurement of intragastric pH

In ten patients found achlorhydric by the titration technique the gastric contents were checked by the intragastric pH tube.

For many years results of intragastric pH measurements have been reported by several authors (EYERLY and BREUHAUS 1939, FLEXNER et al. 1939, EYERLY 1940, ROSSETT and FLEXNER 1943). Technically the most perfect method seems to be the use of glass electrodes as glass is not sensible against the so called „electrode poisons" (ROVELSTAD et al. 1951, SCHMIDT-KESSEN 1955 a). The manufacturing of shatterproof glass electrodes for intragastric use needs special technical requirements; such a special glass electrode is fabricated for the Radiometer apparatus. Our pH tube was prepared with an antimony head according to the descriptions of KREITNER and PANTLITSCHKO (1949) and KINZLMEIER et al. (1951). Its accuracy is less than that of the glass electrodes but still sufficient for clinical use.

The intragastric pH measurements furnished several interesting new data concerning our knowledge of gastric secretory activity. It could be established that the 24 hours, but especially the nocturnal, pH conditions of healthy subjects essentially differ from those of duodenal ulcer patients and persons with anacidity.

(SCHMIDT—KESSEN 1955 b, c). The relation between ulcer pain and actual intragastric pH could also be investigated (WOODWARD and SCHAPIRO 1954). After having „felt" all over the inner surface of the stomach SCHMIDT-KESSEN (1955a) reported to have found several points with low pH values indicating local HCl production in a patient found achlorhydric after 1 mg of histamine. *This fact supports our view that the parietal cell mass is a decisive factor in the assessment of clinical acidity.* Similar results were achieved by KINZLMEIER et al. (1952); with the antimony tube they registered pH 1,8 on a small area in the stomach of a patient with pernicious anaemia. They concluded that small patches of normal mucosa may be present even in cases of anaemia perniciosa with widespread and intensive glandular atrophy.

We tried to find out whether it is possible in any part of the day to reveal some HCl secretion in our achlorhydric patients.

Methods: A small antimony head was applied at hte end of a duodenal tube. Well insulated wires connected the head piece with the pH-meter (type Metrohm). The other electrode was immersed into a dish containing saturated KCl solution. The patient to be examined put his hand into the same dish. The position of the antimony head piece was controlled by fluoroscopy and the distal end of the tube fixed to the mouth. During the day the position of the tube was checked several times. We tried to place the head piece at the bottom of the stomach.

The results are set out in Table 4.

The electrometric readings showed values beneath pH 3 indicating the presence of free HCl in one achlorhydric patient out of the ten. In the other subjects such values were not encountered although temporary lowering of the pH could be registered even in these cases.

The lowest pH readings were ovserved:

1 to 2 hours after lunch	in 3 cases
during the night	in 3 cases
in the late afternoon hours	in 3 cases
in the evening	in 1 case

The changes of intragastric pH readings in two patients throughout the day are depicted in Figure 4.

Conclusions

Histamine seems to be the best stimulant to detect true achlorhydria. The introduction of the augmented histamine test significantly reduced the number of cases thought true achlorhydric. The simultaneous administration of antihistaminics renders the use of big doses of histamine possible. Contrary to our result COMFORT (1951) announced no change in the relative incidence of achlorhydry using the Ewald test meal, alcohol or histamine as the gastric stimulant in the same person. In consequence he is of the opinion that the introduction of histamine did not significantly alter the relative number of achlorhydrics. Our findings are in controversy with this opinion.

We think the effect of larger histamine doses to consist of a more effective mobilisation of the decreased parietal cell mass. The augmented dose of histamine, however, is not sufficient in itself. *Such conditions must be created for the gastric analysis* (fluoroscopic control, recumbent position on the left side, continuous aspira-

Table 4

Intragastric pH values during the day in achlorhydric persons

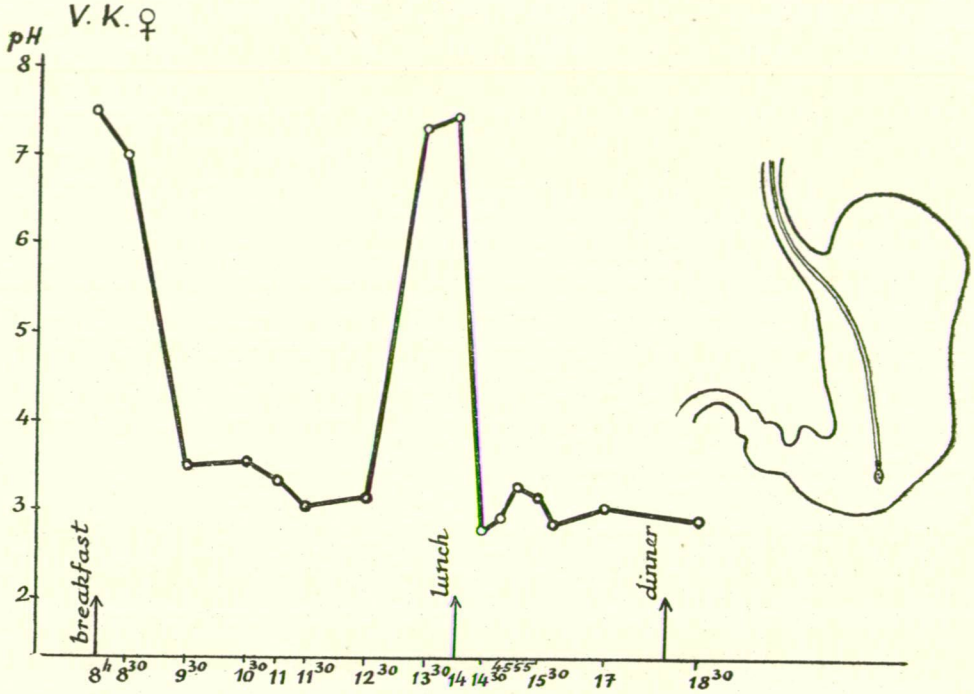
№	Name	T / pH																							Remarks:
1.	G.A. ♂	T	$9^h15'$	$9^h50'$	11^h-	$12^h15'$	$13^h5'$	$15^h20'$	17^h-	18^h-	$18^h30'$	20^h-	22^h-	1^h20	5^h-	7^h										B: $9^h30'$ L: 13^h- D: 19^h- No acid after 1mg of histamine
		pH	7,35	7,10	6,70	6,15	6,50	6,45	4,75	4,2	4,6	5,1	5,4	5,8	7,4	6,8										
2.	G.P. ♀	T	$9^h40'$	$10^h15'$	$11^h15'$	$12^h15'$	14^h-	15^h-	16^h-	$16^h30'$	$18^h30'$	19^h-	21^h-	23^h-	1^h-	3^h-	5^h-	7^h-								B: $9^h45'$ L: $13^h30'$ D: $17^h30'$ No acid after 1mg of histamine
		pH	7.-	6,75	6,62	6,85	6,80	6,32	7.-	6,8	6,32	7,2	6,65	6,9	6,2	6,95	6,35	7,35								
3.	A.B. ♀	T	$7^h50'$	$8^h45'$	$9^h45'$	$10^h45'$	$12^h30'$	$13^h35'$	$14^h5'$	$15^h5'$	$16^h5'$	17^h-	18^h-	$19^h30'$	21^h-	22^h-	23^h-	24^h-	1^h-	2^h-	3^h-	4^h-	5^h-	6^h-	7^h-	8^h-	B: $8^h15'$ L: $13^h20'$ D: $18^h30'$ HCl after 3mg of histamine
		pH	7,45	7,23	7,30	6,15	7,40	5,60	5,55	6,55	6,2	5,60	5,80	6,1	5,65	5,6	5,95	5,65	6,55	7.-	7,95	7,70	7,90	7,45	7,70	7,45
4.	K.V. ♀	T	8^h-	$8^h30'$	9^h30	$10^h30'$	11^h-	$11^h30'$	$12^h30'$	$13^h30'$	$14^h2'$	$14^h35'$	$14^h45'$	$14^h55'$	$15^h15'$	$15^h36'$	17^h-	$18^h30'$									B: $8^h5'$ L: $14^h2'$ D: $18^h5'$ No acid after 1mg of histamine
		pH	7,45	6,95	3,55	3,6	3,44	3,-	3,2	7,20	7,25	2,8	2,87	3,30	3,25	2,8	3,-	2,8								
5.	P.G ♂	T	9^h-	$9^h45'$	$10^h45'$	$11^h45'$	$12^h45'$	$13^h45'$	15^h-	16^h-	17^h-	18^h-	$18^h30'$	19^h-	20^h-	21^h-	22^h-										B: $9^h15'$ L: $13^h50'$ D: $17^h30'$ No acid after 1mg of histamine
		pH	7.-	5,75	6.-	6.-	5,62	4,62	4,62	4,5	4,25	3,25	6,55	7,05	7,15	6,-	5,55									
6.	P.G. ♂	T	$8^h45'$	$9^h20'$	$9^h50'$	11^h-	12^h-	13^h-	14^h-	15^h-	16^h-	17^h-	18^h-	19^h-	20^h-	$20^h30'$	20^h45	23^h-	24^h-	1^h-	2^h-	3^h-	5^h-	6^h-	7^h-		B: $8^h30'$ L: 13^h- D: $19^h30'$ No acid after 1mg of histamine
		pH	6,66	6,10	5,95	6,60	6,90	7,-	6,55	6,7	6,32	6,40	7,22	7,45	6,3	6,6	6,10	6,10	5,9	5,87	6,8	7,7	7,7	7,4	7,25	
7.	S.F. ♂	T	$14^h30'$	$15^h30'$	$16^h30'$	$17^h30'$	$18^h30'$	$19^h30'$	$20^h30'$	22^h-	23^h	24^h-	1^h-	2^h-	3^h-	4^h-	5^h-	6^h-	7^h-	8^h-	$8^h45'$	$9^h30'$	$10^h30'$	$11^h30'$	$12^h30'$		B: $8^h15'$ L: $13^h30'$ D: 18^h- No acid after 1mg of histamine
		pH	6,77	5,87	6,02	6,32	6,77	5,65	4,62	6,55	6,30	7,2	6,55	5,87	6,17	6,45	6,1	6,17	6,45	6,40	6,67	6,10	6,5	5,75	5,35	
8.	S.S.K. ♂	T	$14^h30'$	$15^h30'$	$16^h30'$	$17^h30'$	$18^h30'$	$19^h45'$	$20^h30'$	22^h-	23^h-	24^h-	1^h-	2^h-	3^h-	4^h-	5^h-	6^h-	7^h-	8^h-	$8^h45'$	$9^h30'$	$10^h30'$	$11^h30'$	$12^h30'$		B: $8^h15'$ L: $13^h30'$ D: 18^h- No acid after 1mg of histamine
		pH	5,-	5,15	5,87	5,87	5,20	4,40	5,-	5,37	5,67	5,37	5,15	5,20	5,02	4,6	4,9	5,82	6,80	6,95	5,75	6,45	6,65	5,85	5,85	
9.	M.O. ♀	T	$10^h30'$	$10^h45'$	$10^h50'$	$11^h15'$	12^h-	13^h-	14^h-	$14^h30'$	$14^h45'$	15^h-	16^h-	17^h-	18^h-	20^h-	21^h-	22^h-	23^h-	24^h-	2^h-	4^h-	5^h-	6^h-	7^h-		B: $10^h35'$ L: $14^h10'$ D: $19^h40'$ HCl after 2 mg of histamine
		pH	6,15	6,25	6,25	6,25	6,10	6,10	6,25	6,-	5,8	6,10	6,10	6,50	6,25	6,-	6,10	6,20	6,20	6,1	6,4	6,6	6,6	6,35	6,25	
10.	J.K. ♀	T	10^h-	11^h-	12^h-	13^h-	$14^h15'$	$14^h30'$	$14^h45'$	15^h-	16^h-	17^h-	$18^h30'$	20^h-													B: $10^h10'$ L: 14^h- D: 18^h- No acid after 1mg of histamine
		pH	7.-	7,-	7,03	7,20	6,07	5,65	6,38	6,3	5,20	4,95	5,65	5,60												

T: moment of pH determination, pH: pH value, B: time of breakfast, L: time of lunch, D: time of dinner

Figure 4.

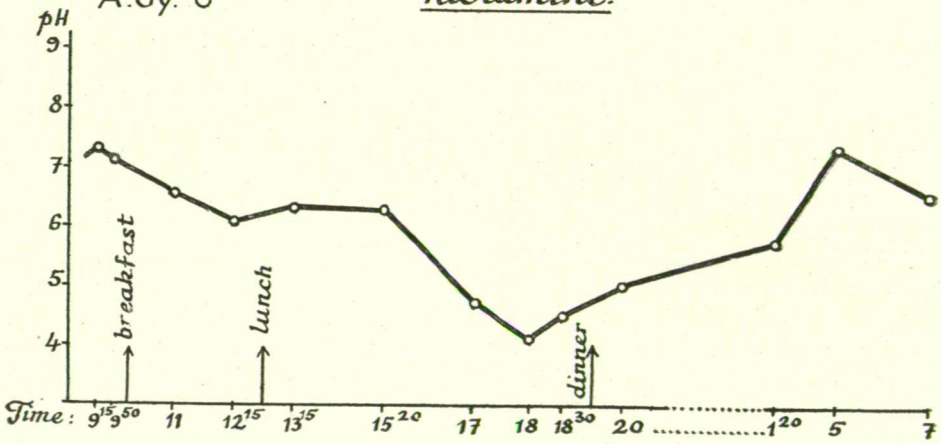
Values of diurnal intragastric pH recordings in a person achlorhydric after 1 mg of histamine.

V. K. ♀



Values of intragastric pH recordings during 22 hours in a person achlorhydric after 1 mg of histamine.

A. Gy. ♂



tion, separate aspiration of the saliva) *which minimize the possibility that small amounts of gastric juice produced escape the attention of the investigator.*

In one of ten achlorhydric subjects we succeeded to demonstrate with intragastric pH measurements low values (< pH 3) indicating HCl production. In the other patients low readings proving the presence of free acid could not be ancountered. The lowest values do not seem to appear regulary in a given period of the day. 60—100 drops of diluted HCl administered during the meals failed to lower the pH of the gastric contents down to the vicinity of 2, optimum pH value for peptic activity. A short-term lowernig of the pH values between 2,5-3,0 could be observed only in two persons out of the six cases examined; the other four presented only minor changes. Two hours after the administration of the diluted HCl solution the pH values were above 5 in all cases.

These results are of importance from the point of view of the therapeutical significance of the HCl treatment. The question will be discussed later in detail in the chapter dealing with „Therapeutic problems" (page: 106).

Disorders of the hydrochloric acid secretion

Normal acid secretion in man is purely a statistical concept. The average acid production of the gastric glands after various stimulants could be asserted using large material. A more abundant acid secretion is designated as superacidity, a smaller one as subacidity. From a physiological standpoint superacidity does not exist because parietal cells are not able to produce HCl of a concentration higher than 170 m Eq. per liter. Free acidity values higher than 120-130 m Eq. per liter are rarely encountered in clinical practice. Much lower values (above 60) are already considered „superacid" by the clinician.

The actual free acidity is the result of an equilibrium between the functioning parietal cell mass and the regulatory (inhibitory) mechanisms. Disturbances may arise from changes of the factors of one or another or both sides.

The correlation between the quantity of the parietal cells and the degree of acidity is verified by histological examinations (TONGEN 1950). Parietal cell hyperplasia may be induced by repeated histamine injections. On the other hand BRENCKMANN's (1929) experiments furnished evidence that the number of functioning parietal cells depends on the intensity of the stimulus used. Far more active parietal cells were demonstrable after histamine than after, e. g. eating. After giving histamine even those areas of the stomach begin to secrete acid which were still quiescent during feeding.

The parietal cell mass available resp. actually functioning represents hence the factor which from the mucosal side determines the acid production. This cell mass is the function of the condition of the gastric mucous membrane; it is increased by hyperplasia, decreased by inflammation or atrophy. The destruction of the cells may be so extensive that the scanty acid secretion cannot be registered on account of its minimal quantity and so achlorhydry may be diagnosed even in the presence of functioning parietal cells. The number of the actually functioning parietal cells depends on the intensity and (perhaps) quality of the stimulus too. The reactivity of the parietal cells is not constant and so it may be assumed (although experimental proofs are still lacking) that acid secretion may be entirely blocked by a functional inhibition of the otherwise intact parietal cells.

The state of the regulatory mechanisms represents the other side of the question. One must take the following factors into consideration:

a) The acid binding property of the mucus. If the meaning of the word „mucus" is not restricted to solid mucoprotein but — according to IHRE (1938) — extended to all substances in the gastric juice exerting an acid-binding, diluting or neutralizing property, the acidity regulating role of the mucus cannot be left out of consideration. Constituents of this complex acid-binding secretion are: 1. the thick, viscous product of the surface epithelium cells, 2. the secretion of the mucous cells of the neck, 3. the alkaline mucous secretion of the pyloric glands and, 4. sometimes in pathological cases, the transudate or exudate of the mucosa. The basicity of this secretion is about 3-11 m Eq. per liter and is due mainly to its bicarbonate content.

The acid-binding property of the mucus is based not only upon neutralisation but also upon adsorption. The importance of the mucus in acid regulation has been emphasized by a number of authors (PAVLOV 1897, LERICHE 1931, MONCEAUX and FONTAINE 1933, HELMER 1934, HENNING and NORPOTH 1932b, MAHLO and MULLI 1934, LAMBLING et al. 1961. etc). BABKIN et al. (1941) determined quantitatively the neutralizing capacity of the mucus. They observed a gastric juice with lower acidity after sham-feeding if the method of stimulating mucus secretion with acetic acid described by GORBUNOVA et al. (1933) was used previously. As the quantity of the juice remained unchanged, the lowering of the acidity had to be ascribed only to increased mucus production.

Mucus seems to play an essential role in acid regulation owing to its neutralizing and adsorptive property. In the case of scanty acid secretion the increased amount of mucus production may result in clinical achlorhydry.

b) Duodenal regurgitation. Its frequency and the possibility that it may stimulate the fasting gastric secretion was already emphasized. To PAVLOV (1897) and BOLDYREFF (1907) goes the credit for the description of a regular duodenal regurgitation after feeding of fat. In Boldyreff's opinion duodenal regurgitation serves for the „autoregulation of gastric acidity". According to HETÉNYI and VÁNDORFY (1922) if duodenal regurgitation meets with difficulties an increase in acidity ensues. The problem was submitted to a thorough examination by WILHELMJ et al. (1935). They observed at the end of the secretory period the entrance of a non-acid juice of duodenal origin into the stomach. As this juice was of low alkaline range (of 0,04 normality), they concluded the decrease of acidity to be due in 75 per cent to dilution and only in 25 per cent to neutralisation.

KATSCH et al. (1935) are of the opinion that alkaline gastric contents represent the strongest stimulus for duodenal regurgitation. This assertion could be confirmed by our own observations. We found the bilious coloring of the achlorhydric gastric contents to be almost regular, this juice turning colorless at the beginning of HCl secretion.

It is advisable to take a technical circumstance into consideration. As the pressure gradient between the antrum and duodenum takes a prominent part in the activity of the pylorus, gastric aspiration may contribute to duodenal regurgitation. It is important not to forget this fact while studying the mechanism of regurgitation. Differences should be appreciated only on the basis of control experiments performed with the same sort of aspiration technique.

c) Saliva. Its secretagogue effect in the fasting stomach has already been mentioned. In some species (e. g. sheep) saliva has a decisive role in in the neutralisation of gastric acid. In man swallowing of saliva may contribute to the lowering of acidity at least as a diluting factor. Its quantity is not to be neglected, a fact which is well shown by the cryoscopic index of the gastric juice. This is about —0,47 in the mixed gastric

contents, while that of the pure gastric juice is between —0,55 and —0,62. As of all juices in question only saliva has a cryoscopic index (appr. —0,2) which differs substantially from that of the pure gastric juice and the blood, it is obvious that the difference mentioned above cannot be caused but by the admixture of saliva.

The quantity of the saliva produced may sometimes be quite considerable; this could be demonstrated by continuous gastric and salivary aspiration. Our data indicate that *the diluting effect of the saliva may be of importance especially in patients with scanty gastric secretion.*

The quantity and pH values of the saliva were recorded during gastric aspirations of 40 achlorhydric, 26 subacid and 17 normacid subjects.

Methods: A dental type of suction apparatus was set into action paralelly with the gastric aspiration. During the continuous aspration the CO_2 content of the saliva decreases; our values, indeed, are higher than those registered *„in situ"*, which can be explained by the CO_2 loss (OSTER et al 1953).

The quantities and pH values of the saliva collected during 90 minutes are shown in Tables 5 and 6.

No significant changes in the quantities of the saliva could be observed in the various groups. The average quantity of the achlorhydric group was 21,6 ml, those of the subacid and control group 30,4 resp. 27,3 ml. In the achlorhydric subjects this 20 ml of saliva may be of importance as a diluting factor if swallowed. Persons with a gastric secretion of 10-20 ml during the 90-minute-period are not infrequently encountered among the achlorhydric patients. In such cases the admixture of 20 ml of mostly neutral saliva may significantly dilute the scanty acid secretion produced. This can be demonstrated on the following example. A gastric juice with a 0,01 N HCl content has a clinical acidity of 10 units; if this fluid is diluted with the same quantity of saliva, the normality of the juice will change to 0,005 (i. e. 5 mN) with a clinical acidity of 5 units. This happens merely on account of dilution not taking into consideration the eventual bicarbonate content of the saliva.

No difference was observed as to the pH values of the saliva in the achlorhydric, subacid resp. control groups. Perhaps it is worth mentioning that while the distribution of values above and beneath pH 7,0 are nearly equal in the subacid and control groups, in the achlorhydric group the rate of subjects with pH values above 7,0 is considerably higher.

Summing up of data concerning the pH values of the saliva aspirated:

	Total number	<pH 7	>pH 7
Persons with normal acidity	15	6	9
Subacid subjects	26	14	12
Achlorhydrics	40	12	28

d) The existence of sympathetic inhibitory fibres for the stomach is a problem videly discussed in the literature. The possibility arose namely that the supersecretion caused by vagal hyperactivity may have a subsecretory counterpart based on symphathetic predominance. BICKEL (1925) described a double sympathetic innervation of the stomach: excitatory and inhibitory. The inhibitory effect of the sympathetic fibres could not be proved experimentally. BAXTER (1934) observed a scanty mucus secretion after splanchnic stimulation in the dog and the cat; he supposes that the sympathetic excitation would result in a stimulation of the mucus cells of the neck. SAFIROV (1953) describes a spontaneous gastric secretion in the

Table 5.

Quantity and pH values of the saliva collected in the achlorhydric group.

	№	Quantity of the saliva	pH	Remarks
1	1	26	7,3	HCl after 2 mg of histamine
2	2	14	7,9	pernicious anaemia
5	3	24	7,0	pernicious anaemia
16	4	64	7,7	HCl after 3 mg of histamine
24	5	64	5,9	
29	6	42	5,9	
40	7	15	6,2	
41	8	36	5,6	
43	9	6	6,0	
44	10	23	5,7	
45	11	33	6,6	HCl after 3 mg of histamine
46	12	46	5,6	HCl after 2 mg of histamine
47	13	16	5,8	HCl after 3 mg of histamine
48	14	18	7,6	HCl after 3 mg of histamine
49	15	24	5,7	
50	16	40	6,0	
51	17	48	6,0	HCl after 3 mg of histamine
52	18	20	8,1	
53	19	9	5,9	HCl after 2 mg of histamine
55	20	13	7,0	No HCl after 3 mg of histamine
56	21	38	7,4	
57	22	13	7,2	
58	23	18	7,2	pernicious anaemia
59	24	7	7,1	No HCl after 3 mg of histamine
60	25	11	7,0	pernicious anaemia
61	26	36	7,0	pernicious anaemia
62	27	30	7,2	No HCl after 3 mg of histamine
63	28	5	7,2	HCl after 3 mg of histamine
64	29	20	7,2	HCl after 2 mg of histamine
65	30	20	7,0	No HCl after 3 mg of histamine
66	31	31	7,3	pernicious anaemia
67	32	8	7,0	
68	33	6	7,0	
69	34	11	7,0	No HCl after 3 mg of histamine
70	35	28	7,3	
71		non measurable		pernicious anaemia
72	36	4	7,8	pernicious anaemia
73	37	4	7,4	No HCl after 3 mg of histamine
74	38	7	7,2	pernicious anaemia
75	39	5	7,0	
76	40	3	7,3	No HCl after 2 mg of histamine

Table 6.

Quantity and pH values of the saliva collected in the subacid and normal group.

	№	Quantity of the saliva	pH		№	Quantity of the saliva	pH
12.	1.	5	6	3	1	4 1	6,8
14.	2.	2 0	5,3	8	2	2 2	6,0
15.	3.	2 2	5,5	11	3	8	7,0
16.	4.	1 1	5,1	15	4	4 8	7,0
17.	5.	2 0	5,3	16	5	5 6	6,0
18.	6.	4 0	6,7	17	6	4 3	6,8
20.	7.	3 2	6,0	19	7	9	5,9
21.	8.	2 7	6,2	22	8	8 0	7,0
22.	9.	1 4	7,8	27	9	1 3	7,0
23.	10.	1 1 0	5,4	28	10	1 0	7,0
24.	11.	8 0	7,4	29	11	5	7,0
25.	12.	1 1	6,9	30	12	4 4	6,9
26.	13.	4 1	6,7	32	13	2 2	7,0
27.	14.	1 4	6,5	33	14	4	7,0
28.	15.	2 8	6,6	34	15	5	7,9
29.	16.	4 4	7,0				
30.	17.	3 0	7,0	31	16	in traces only	non measurable
31.	18.	3 6	6,8	26	17		
33.	19.	2 0	7,2				
34.	20	3 0	7,4				
35.	21	6	7,0				
36.	22.	2 0	7,1				
37.	23.	1 5	7,0				
38.	24.	3 5	7,3				
39.	25.	3 5	7,2				
40.	26.	5 6	7,0				

dog after the removal of the solar plexus. OBERHELMAN and DRAGSTEDT (1951) observed an increase of both the quantity and the acidity of the gastric juice aspirated after bilateral sympathectomy and splanchnicectomy; simultaneous vagotomy did not alter the situation. They concluded that the sympathicus contains inhibitory fibres. The histamine sensitivity of gastric structures increased by 50-80 per cent; an interesting finding made by the same authors. The inhibitory effect of the sympathicus was reported also by SHAFER and KITTLE (1951). Prolonged stimulation

of the vagal fibres resulted in irreversible atrophy of the gastric mucosa (RUDIK-LAZOWSKY 1948).

e) Inhibitory effect of humoral factors. It has been known for a long time (EWALD and BOAS 1886) that gastric secretion and motility is inhibited by neutral fats. This inhibition is not the result of a direct contact of fat with the gastric mucosa but follows the presence of fat in the duodenum resp. the upper part of the jejunum.

As the inhibitory effect of fat-feeding may be observed also in autotransplanted i. e. completely denervated stomach (FARREL and IVY 1926, FENG et al. 1929), and intravenous injection of the fatty chylus does not produce it (FENG et al. 1929), the humoral character of the inhibition became evident. The hormone was called *enterogastrone* by KOSAKA and LIM (1930). Enterogastrone is able to inhibit all sorts of gastric secretion irrespective of the nature of the stimulation (LIM 1934). Particulary the quantity and the acidity of the secretion decreases; the output of neutral chloride and mucin does not change significantly. Peptic activity decreases, an effect which may be abolished by vagotomy. The inhibitory effects on secretion and on motility seem to be separable.

The natural inhibitory hormone of the small intestinal mucosa has undoubtedly an important role in the physiological regulation of acidity. We do not possess, however, any experimental proof to assume that anacidity or even a low grade subacidity may be produced by enterogastrone, nevertheless theoretically the possibility is not excluded.

In case of fats the decrease of acidity may arise not only by enterogastrone mobilisation but also by an increased duodenal regurgitation as already mentioned.

Some authors maintain that the gastric juice itself contains a secretion inhibitory material. So BRUNSCHWIG et al. (1942) described such a substance in the normal gastric juice. The same factor could be detected in the gastric juice of pernicious anaemia and achlorhydic gastric cancer patients in a far greater quantity. Persons with simple anacidity possessed less of it but still more than the normal subjects (BRUNSCHWIG et al. 1939, 1940). Similar findings were reported also by BLACKBURN et al. (1950). With intravenous injections of normal gastric juice, a pronounced atrophic gastritis has been induced in dogs (SMITH et al. 1960), and gastric HCl production has been significantly lowered in pylorus-ligated rats (MENGUY and SMITH 1960).

The problem whether under pathological conditions some products of the gastric mucosa may affect the development of achlorhydry is an unsolved one. The experiments of BRUNSCHWIG need further affirmation. The frequency of achlorhydry in the cases of relatively small malignant growths which do not destroy substantial parts of the gastric mucosa is a rather delicate question. One may assume the presence of a secretory depressant produced by the gastric mucosa which exerts an inhibitory effect on gastric secretion. A similar mechanism may function in the case of pernicious anaemia too; the inhibitory material diminishes the secretion, areas with low secretory activity become atrophic. Experimental proofs of these speculations, however, are still lacking.

Mucosal atrophy with subsequent achlorhydry in the digestive system may be produced in experimental animals by hypophysectomy and adrenalectomy (HAEGER et al. 1953). The role of the neuroendocrine factors in the development of human gastric atrophy is hitherto unknown. As mentioned, RUDIK-LAZOWSKY (1948) succeeded in producing irreversible gastric atrophy through long-standing vagal irritation.

f) Some other factors. Hydrochloric acid itself has a strong inhibitory effect on subsequent gastric secretion. This effect is not bound to HCl as it may be brought about by other acids, even by organic ones (e. g. acetic acid VÁNDORFY 1924, 1925); it is important, however, that the acid should be of a certain concentration.

Among the factors influencing HCl secretion changes in the CO_2 tension of the blood should be mentioned as well. The increase of the gastric secretion during hyperventillation could have been established experimentally. By increasing the CO_2 content of the blood a simultaneous increase of gastric secretion could be observed. It was proved that the CO_2 tension exerted this effect directly not through changes in the blood pH values. The posthistaminic secretion is not inhibited either by hyperventillation or by acidosis (BROWNE and VINEBERG 1932). If the lowering of the CO_2 content of the plasma or acidosis is present before the commencement of the secretion, histamine does not exert its secretion-stimulating effect. This finding was confirmed by DELRUE (1934) in Switzerland on the Jungfrau-Joch. He stated that dogs had a lower secretion rate and acidity on the summit (3460 m) than when brought to sea level. PICKET and VAN LIERE (1939) maintain that the secretion-decreasing effect of the anoxia operates through vagal channels; dogs with Pavlov pouch are highly sensitive to anoxia. Vagus stimulation seems to be unable to evoke secretion under a 30% CO_2 tension, which is not the case with histamine. According to APPERLY and CRABTREE (1931) it is the plasma bicarbonate level which regulates gastric acidity. Similar correlations were found by LURJE (1927), MOSONYI et al. (1935) and KURTZ and CLARK (1947).

The high energy demand and the apparent vulnerability of the parietal cells would justify the development of achlorhydry in case of a significantly decreased gastric mucosal blood supply. Ligation of the gastric arteries in man, however, does not seem to be an effective measure to control HCl secretion (SOMMERWELL 1948). According to our own observations ligation of the main gastric arteries in dog does not produce gastric acid deficiency, on the contrary, here and there a marked parietal cell hyperplasia (endogene histamine liberation?) has been observed (VARRÓ and SZARVAS).

Finally it should be mentioned that the gastric mucosa contains an urea-splitting enzyme, the urease, which produces ammonia from circulating urea. It is supposed that the ammonia formed by the urease participates in the neutralisation of HCl; this process should occur intracellularly (FITZGERALD 1946).

V. TRANSFER OF NEUTRAL RED INTO THE STOMACH

Survey of the literary data.

The elimination of the dye, neutral red by the gastric mucosa was first described by FULD (1908). Its use was introduced into gastroenterologic diagnostic procedures by GLAESSNER and WITTGENSTEIN (1923). In their view a parallelism may be demonstrated between the acidity and the neutral red content of the gastric juice.

The procedure consists of the injection of a 1 per cent solution of neutral red either intravenously of intramuscularly. In the original description (and this was later followed by several other authors) the intramuscular route was employed. To avoid the eventual fluctuations of the absorption some authors prefer to inject the dye intravenously, which necessitates, however, a completely pure solution of the dye. Neutral red is an indicator dye having a pH range of 6,8 to 7,4. It has a yellow colour in alkaline and a red one in acid media. The dye may be easily recognized in the gastric juice by its colour but methods for quantitative determination have also been worked out (KOLM et al 1949, JÁVOR 1956).

Later it could be verified (WINKELSTEIN and MARCUS 1929, BERKESY 1929, HENNING 1932, GILLMAN 1944 etc.) that the appearance time of the dye in the gastric juice is shorter in cases of superacidity or normacidity than in cases of subacidity. In cases of achlorhydry the dye was generally not to be detected, although sometimes a red colouring was observed even in gastric juices containing no HCl.

Most authors (GLAESSNER and WITTGENSTEIN 1923, KATSCH and KALK 1926b, HENNING 1932, MORRISON 1935–36, GILLMAN 1944 et al., KOLM 1945) were of the opinion that neutral red is excreted through the parietal cells.

Investigations to study the excretion of neutral red were, however, not uniformly performed. Some injected the dye during the fasting state, other workers administered it along with a test meal, caffeine, or histamine. Neutral red secretion was observed most consistently when administered with histamine, a fact which was thought to be indicative of a close connection with the parietal cells resp. the acidity. This observation could be confirmed in animal experiments as well. So KOBAYASHI (1925) and later MARUNO (1935) described an identical influence of various stimuli (pilocarpine, atropine, vagus stimulation) on both neutral red and acid secretion. OBRINK (1948) using constant continuous intravenous histamine and neutral red injections came to the conclusion that the neutral red secretion does not depend on the secondary i. e. actual acidity of the stomach but is rather in close correlation with the primary acidity, i. e. the HCl produced by the parietal cells. KOLM et al. (1945) also concluded that the excretion of the dye is a function of the parietal cells, and peptic resp. mucoid cells have no role whatsoever in this process.

One may encounter, however, other opinions too. DAWSON and IVY (1925) maintain that the pyloric part, too, is capable of excreting neutral red. On the ground of their clinical experiences DAIKOVSKY and SOLOVEI (1934) share this opinion. According to PIERSOL et al. (1925) and BOCKUS (1944) the whole of the glandular mass of the stomach – especially the antral part – participates in the excretion of neutral red; the suggest the possibility of using the appearance of the dye as an inidicator for the presence of the intrinsic factor.

The problem of neutral red secretion has a practical importance in the assessment of achlorhydry. GLAESSNER and WITTGENSTEIN (1925) described that no neutral red appeared in the gastric juice of seven anacid patients (Ewald test meal). In cases of pseudoachlorhydry (i. e. HCl secretion only after histamine) neutral red secretion could be always detected by KATSCH and KLAK (1926); out of 13 patients with histamine-refractory achlorhydry (after 0,5 mg of histamine) the dye made its appearance only in 2 subjects. According to DAVIDSON et al (1925) neutral red does not appear in patients with pernicious anaemia, whereas it can be regularly detected in cases of secondary anaemia and other achlorhydrias. They were the first to try to release the dye from the mucosa by acid instillation (with 0,025 n HCl) but without success. Later DAVIDSON (1925) claimed to have found reddish discoloration after washing thorougly the stomach with acidized water in every case expect in patiens with pernicious anaemia.

According to WINKELSTEIN and MARCUS (1929) positivity of the neutral red excretion test would prove the capacity of the mucosa to secrete HCl even if actually no HCl production occurs. They considered the appearance of the dye an indicator of the integrity, but not necessarily of the actual activity, of the parietal cells. The method worked out by WINKELSTEIN (1942) necessitates the simultaneous administration of histamine and neutral red with an ordinary test meal. When neutral red appeared but no HCl was present, the patient was qualified as temporary (pseudo) achlorhydric. He emphasized the possibility of neutral red excretion without simultaneous acid production and considered the test meal combined with neutral red administration a more sensitive procedure concerning the functional integrity of the acid producing cells than the ordinary histamine test. KATSCH and KALK (1926) insist on the neutral red excretion to be a part of the complexe secretory function of the mucosa. The most sensitive function of the mucosa would be the acid production; after losing this capacity the glandular cells would still be able to secrete neutral red. The secretion of chloride and fluid would be less sensitive; the most primitive reaction of the mucosa would represent the production of an aqueous-mucous fluid. LURJE and MOGILEVSKI (1928) maintain that the neutral red test has the special advantage of giving information of the secretory capacity of the stomach without influencing its motility. Finally ZELDINA and BYKOV (1949) think that neutral red secretion and HCl production take place quite independetly.

In HENNING's opinion (1934) based on his previous experiments (HENNING and JÜRGENS 1930) parietal cells may preserve the ability to secrete the dye even after the cessation of HCl production. No neutral red exretion occurred in patients with anaemia perniciosa or with other sorts of gastric atrophy; he concluded, therefore, that the negativity of the neutral red test would indicate the presence of atrophy. They observed no difference in the appearance time of the dye in patients with various degrees of acidity. The secretion of HCl may be subject to inhibition and in such cases the neutral red test may be helpful in differentiating functional and organic achlorhydries. ALLODI and QUAGLIA (1936) controlled the neutral red excretion in 65

patients with achlorhydria and compared the results with those of the histamine test. They described dye appearance also in some subjects found histamine refractory achlorhydric. In their view none of the tests can make up for the other. SCHEMENSKY and GELING (1931) found dye excretion in only 5 out of 111 patients with histamine refractory achlorhydry, whereas 39 pseudo achlorhydrics out of 55 had positive neutral red tests.

GILLMAN (1944) believed that the neutral red test is of diagnostic value itself and need not be combined with histamine injection; neutral red and HCl secretion would represent two independent functions of the mucosa. In his cases with no neutral red excretion histamine could not provoke HCl secretion. This is most surprising since KOLM et al. (1945) demonstrated that neutral red excretion could be elicited by histamine even 6 hours after the administration of the dye. KOMAROV et al. (1947) pointed out that neutral red may be secreted not only by the stomach but also by the liver. Thus duodenal regurgitation may inject into the stomach dyestuff which has nothing to do with the function of the gastric glands. LERNER et al. (1942) observed with the aid of gastroscopy that neutral red is secreted by the upper part of the fundus and corpus. No dye secretion could be revealed in the cardia, pylorus or antrum.

We performed similar experiments in dogs by means of our intestinal cannula-method (VARRÓ and JÁVOR 1955). Pointlike dye excretion described by LERNER et al. (1942) could not be observed either with neutral red or with methylene-blue. The colour of the red dye could hardly be distinguished from that of the mucosa so that the moment and exact site of its appearance could not be ascertained. Most frequently it was the red pool on the bottom of the stomach which caught the eye. Otherwise the intestinal cannula method offers a far better possibility to examine the gastric mucosa *in vivo* than gastroscopy.

Extensive examinations were performed by HALLÉN (1949) to decide whether the stomach is capable of secreting neutral red without HCl. He took the explicit point of view that neutral red secretion means *always* simultaneous HCl production. In cases where former workers were unable to demonstrate the acid, the results might have been influenced by technical difficulties arising from the minute amount of HCl produced. In his view the neutral red test is very suitable for differentiation of various kinds of achlorhydria; where neutral red appears in the gastric juice the achlorhydria is not a true one. According to him the neutral red refractory cases may be divided with the aid of acid instillations (150-170 mN HCl) in two separate groups. Dye is secreted into the acid instillate in the first group but not in the second. Sometimes he succeeded in demonstrating the dye even in instillates of some patients with pernicious anaemia (in 5 out of 35). He considers the cases with no neutral red in the instillate to be the most serious forms of mucosal lesion. The fact, that in most cases the appearance of the dye could be elicited only with HCl of high acidity but not with instillates of lower (e. g. 120 mN HCl) acidity, would mean that neutral red excretion is bound to HCl secretion of high acidity.

Investigations concerning neutral red secretion

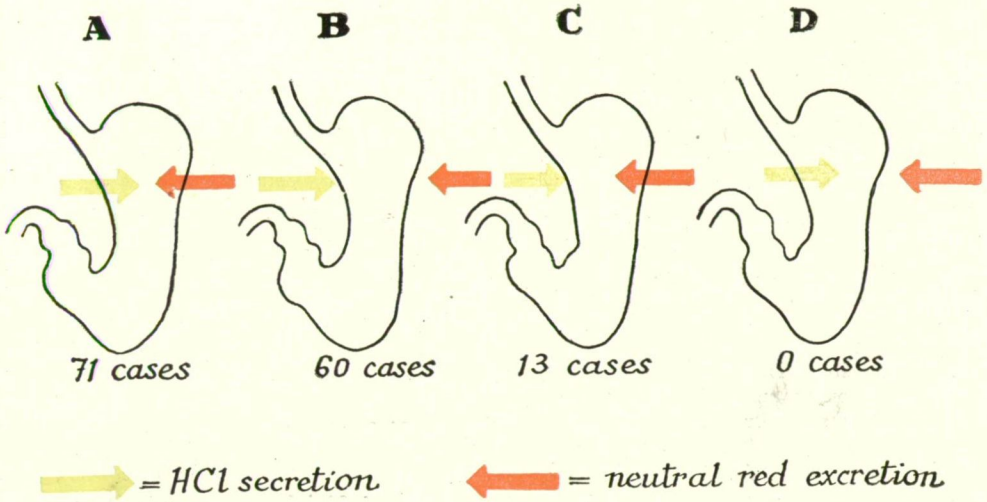
Investigations of the neutral red excretion after histamine administration were carried out in 144 patients.

In 71 cases both acid and neutral red appeared in the gastric juice. (Figure 5 A). In 12 of them neutral red could be demonstrated already at a lower histamine dose than did the acid, thus indicating its forthcoming appearance. In the other cases acid and dye could be found after the same dose of histamine. In 60 cases neither acid nor neutral red could be observed. (Figure 5 B).

Figure 5.

Neutral red excretion into the stomach in achlorhydric patients after various doses of histamine.

144 cases



In 13 patients one or the other dose of histamine was followed by the appearence of neutral red in the gastric juice but HCl could not be detected. (Figure 5 C). Only a 1 mg dose of histamine was given to two patients; the dye did appear but the acid did not. Whether they would have reacted with acid production on a higher histamine dose we cannot say.

Case reports of the other 11 patients are given in the following:

1. I. H. male. No acid or dye secretion was seen after the injection of 1 mg, then of 2 mg of histamine. The gastric juice was biliously discoloured with a lowest pH of 6,25. Enzyme production was maintained. After administration of 3 mg of histamine: fractions 1 and 2 obtained at the first and second 15-minute intervals did not turn Congo paper blue, mucus: 3 plus. Fraction 3 was white in colour, mucus: 3 plus, pH: 5,10. The characteristic pink colour appeared in fraction 4; pH: 3,95. Fraction 5 was pink with pH of 3,50 and fraction 6 was equally pink with a pH of 3,95.

On laparotomy, the gastric mucosa presented the picture of hypertrophic gastritis. The patient had chronic pancreatitis, and this was verified histologically.

2. M. T. female. Neutral red was employed only with the 3 mg dose. Because of technical difficulties no pH values could be recorded in this case. The amount of emptied gastric juice was minimal with a total of 8 ml for all six fractions. Fractions 5 and 6 were faintly pink, Congo paper was unchanged. It should be noted that at the examination with 2 mg when dye had not yet been given, the pH of fraction 4 was 3,75. The patient's achlorhydry could not be brought into relationship with any disease. Gastroscopy revealed atrophic mucosa.

3. P. P. male. Neither acid nor neutral red was seen after injection of 1 mg of histamine. Minimal pH recorded was 7,15; the gastric juice was bilious and mucous. After injection of 2 mg of histamine, fractions 5 and 6 were strongly mucous, unfiltrable and

pale pink in colour. In these fractions no bile was to be seen. The pH of fractions 1 to 4 (poured together) was 7,33; that of fraction 5 was 6,60 and that of fraction 6, 5,30. After 3 mg of histamine neither acid nor neutral red appeared. The gastric juice was strongly mucous and bilious.

Clinical diagnosis: polyposis, carcinoma with multiple polyps (verified by operation and histological examination).

4. V. Ty. male. First 1 mg of histamine, later 2 mg were given without neutral red or acid appearance. There was emptying of bilious, mucous gastric juice with a high pH. After 3 mg of histamine for a few seconds at the beginning of fraction 4 a pink juice could be observed, the rest of this fraction being bilious. The pH of fraction 4 was 6,10; that of fractions 5 and 6, 7,4. We resorted even to a 4 mg-dose of histamine without success. Gastroscopy revealed a normally hyperaemic mucosa somewhat smoothed away; there was no pronounced atrophy.

The cause of this patient's achlorhydry could not be found. He was discharged and remained free of complaints, although he had previously suffered for years from diffuse pain in the stomach area.

5. M. I. male. No acid or neutral red after 1 mg of histamine. After 2 mg a pink colour was detected at the end of fraction 3 and at the beginning of fraction 4. The pH of fractions 3 and 4 were 6,30 and 6,68 resp.; the gastric juice was strongly mucous and the amount was small. After 3 mg of histamine fraction 3 was only pale pink but fractions 4, 5, 6 were markedly red. The following pH values were recorded: fraction 3, 5,40; fraction 5, 3,70. Strongly mucous gastric content of scanty quantity (not more than 13 ml in 90 minutes).

6. F. B. male. After 2 mg of histamine neither acid nor neutral red appeared. After 3 mg fraction 6 is pale pink, mucus: 3 plus, its amount: 3 ml, its pH: 5,5. The total amount of the strongly mucous gastric juice collected during 90 minutes was 21 ml. The acid instillation test after neutral red injection (description see later) was positive. Gastroscopy: patchy atrophy.

7. L. D. female. After 3 mg of histamine fractions 5 and 6 were pale pink, their quantity being 4 and 0,5 ml, resp. Mucus: 3 plus. The acid instillation test after neutral red injection was positive.

8. I. M. female. After 3 mg of histamine fractions 4 and 5 are pale pink; their amount 4 and 2 ml, resp. Mucus: 2 plus. Acid instillation test after neutral red injection positive. Gastroscopy: normal mucosa with small islands of atrophy.

9. I. J. female. After 2 mg of histamine fractions 3, 4, 5, 6, are markedly pink; their amount 5, 6, 6, 3,5 resp. Mucus: 2 plus. The pH value of the fraction 5 is 3,2(!).

10. B. K. male. No acid and neutral red after 1 mg of histamine. After 3 mg, fractions 2, 3, 4 are pink; their amount 9, 7, 8 resp. Mucus: 1 plus. The pH values were: fraction 2-4,6; fraction 3-5,2; fraction 4-4,4. The acid instillation test after histamine injection was positive.

11. F. C. female. No acid or neutral red secretion after 2 mg of histamine. After 3 mg fractions 4, 5, 6 are pink; their amount 4, 3, 3, ml resp. Mucus: 1 plus. pH of fraction 6 was 5,7. Acid instillation test after histamine injection positive.

It may be interesting to report one of our cases, where no acid could be detected after 3 mg of histamine but the dye made its appearance. The pH value of the pink gastric juice was 4,5. A second test with 3 mg of histamine revealed the presence of both HCl and neutral red.

Not a single case could be detected where simultaneously with HCl secretion, neutral red failed to appear in the gastric juice. (Figure 5 D).

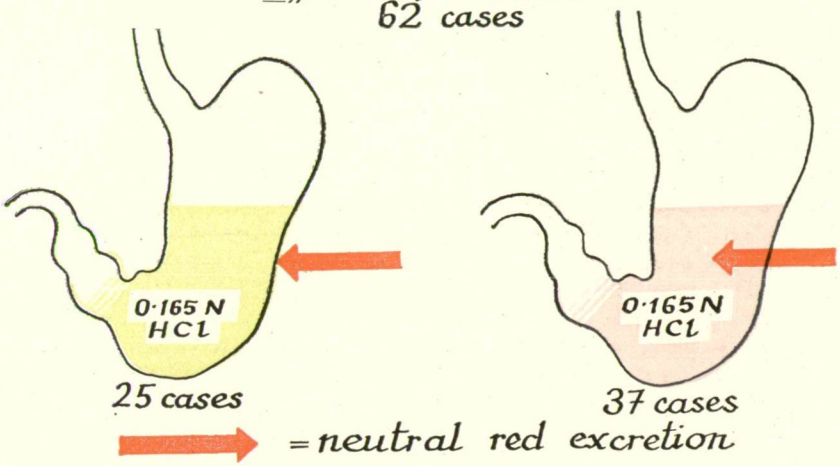
Examinations were performed also in 20 patients of our „subacide" group. We succeeded in detecting the dye in the gastric juice in 19 of them. In one person the evaluation of the gastric juice was disturbed by bilious regurgitation.

Finally 16 subjects with normal acidity served as controls: neutral red was excreted in all of them.

Figure 6.

Results of the acid instillation test after neutral red injection in histamine refractory achlorhydric patients.

62 cases



The average lengths of time that elapsed before the appearence of neutral red in the gastric juice was examined in the various secretory groups. The results were as follows:

Achlorhydric group:	average 38 minutes (range 10-75 min.)	19 cases
Subacid group:	average 37 minutes (range 15-70 min.)	18 cases
Normacid group:	average 15 minutes (range 8-30 min.)	16 cases

The acid instillation test after neutral red injection

The acid instillation test after neutral red injection was performed in 62 achlorhydric patients.

Method: The duodenal tube was introduced under fluoroscopic control and the patient received 10 mg of morphine subcutaneously to prevent duodenal regurgitation. The stomach was washed out with HCl to remove incidental bilious content. Then 5 ml of 1 per cent neutral red were injected intramuscularly and, after a 15 minute period, 100 ml of 165 mN HCl was administered by injection through the duodenal tube to the patient lying on his left side. Samples of 5 ml were taken every 10 minutes for 90 minutes and the time of appearance of the dye was carefully noted.

The neutral red passed over into the instilled acid in 37 cases and did not do so in 25 cases (Figure 6). Of the 25 negative cases 15 were patients with pernicious anaemia. In the positive cases the time of appearance of the dye varied between 10 and 40 minutes.

Discussion

Our investigations strongly support the view that the appearance of the neutral red in the gastric juice depends on HCl secretion. In the cases where after one or

more mg of histamine HCl production occurred, there was always a simultaneous dye excretion as well.

Regurgitation of the bilious duodenal contents no doubt may disturb the evaluation. It could be inhibited with absolute certainty only by applying a tube with a double lumen through which a simultaneous aspiration from both the stomach and duodenum could be achieved. The execution of this method is, however, very difficult, time-consuming and sometimes even impracticable which renders its use as a routine procedure impossible. Neither do we think that the obstruction of the pylorus by a balloon represents a useful method to prevent regurgitation. That is why the administration of morphine prior to the examinations is of great importance; it prevents regurgitation of bile in all likelihood by inducing pylorospasm. Anyhow the instilled acid usually remains colourless during the entire period of the test.

In connection with duodenal regurgitation the question arises whether achlorhydry respectively acidity influences the activity of the pylorus. According to the classic concept of CANNON (1904) pyloric activity is regulated by the acid content of the stomach and the duodenum. This opinion was attacked later by several authors. So MCCLURE et al. (1920) declared that they found no relation between the acidity and gastric evacuation; the activity of the pylorus was not influenced by constant pH conditions in the duodenum. Some observers even maintain that X-ray examination of the stomachs of patients in whom the pylorus has been excised, shows emptying times which do not differ significantly from normal. According to modern views the immediate factor which would determine the rate of gastric emptying (respectively the duodenal regurgitation) appears to be the pressure gradient between the stomach and the duodenal bulb.

We did not examine the problem of gastric emptying, but want to refer to some observations regarding the regurgitation and the pyloric activity. We could notice namely a certain correlation between the bilious regurgitation and the beginning of acid secretion. At the beginning of the HCl secretion the bilious colouring of the gastric juice turns pink, later red or even lilac depending on the concentration of neutral red. If this juice is filtered, the dye remains on the filter-paper and the filtrate becomes colorless indicating that no significant duodenal regurgitation occurred after the beginning of acid (and neutral red) secretion. Sometimes the acid and neutral red secretion is only of short duration, then simultaneously with the anacidity the bilious regurgitation reappears. The filtrate of this juice is no longer colourless but greenish yellow.

As our investigations were carried out with constant (continuous) suction, a constant negative pressure was maintained in the stomach as compared to the duodenum. Thus optimal conditions for the duodenal regurgitation were given during the whole duration of the examination. In spite of that it could be observed that in normacid and subacid subjects the regurgitation ceased at the beginning of an acid secretion of red colour and indeed the filtrate of this juice did not contain bile pigment. In our view this cannot be explained otherwise but with the closing of the pylorus. When the acid secretion stopped, the bilious discolouring reappeared.

We think therefore, that the conditions of gastroduodenal acidity represent an important — although not exclusive — factor of the regulation of the pyloric activity. The same experience was reported by KATSCH et al. (1935) who described the alkaline gastric contents as the strongest stimulus for the duodenal regurgitation.

On the other side in our animal experiments (JÁVOR and VARRÓ 1957, VARRÓ et al. 1959) we could ascertain that the „custodian of the gate" (*πύλη οὖρός* means guard

of the gate) does not play a passive role only, is not merely a canal between the antrum and the duodenum through which the gastric resp. duodenal contents pass according to the actual pressure gradient between the two structures. We examined namely the inside of the stomach in dogs with the aid of our intestinal cannula method. The method consists of pushing through a cannula into the stomach of a living, waking dog the tube of a rectoscope through which the inside of the stomach may be studied. We could always gain the pylorus with the rectoscope but were able to pass through only occasionally in spite of vigorous insufflations. The strong muscular ring of the pylorus resisted the pressure applied. Naturally the experiment does not exclude the possibility that the pressure gradient may possess an important role in the regulation of the pyloric activity but in any case it furnishes evidence that the pylorus may contract even against a significant pressure gradient.

It seems particularly interesting that in 12 cases the neutral red indicated already after a small dose of histamine that HCl would appear after a larger histamine dose. In our opinion this can be explained by the fact that even minimal amounts of HCl secreted for a short time might have been sufficient for the dye to get into the gastric juice. The pH of the entire 15-minute fraction rises above 3 as a result of the effect of diluting and buffering factors but does not surpass 7, thus the original red colour of the acid form of neutral red remains unchanged. In other words the acid form of the dye preserves its red colour even in higher pH ranges (turning yellow between pH 6,8-7,4), but can gain entrance into the gastric juice *only in the case of (no matter how minimal) HCl secretion.*

Our experimental observations support this view. We occasionally observed a fall of the gastric pH to below 3, sometimes for seconds only; afterwards it remained over 3 during the whole time of the examination either because of alkaline components or the cessation of acid secretion. In these experiments a small glass attachment containing a small piece of Congo paper was applied to the aspiration tube. In some cases when the Congo paper suddenly turned blue we removed it, put in a new paper, but the next portions of the gastric juice no longer had any blueing effect. In this way we succeeded in demonstrating a transitory acid secretion even in those cases where no HCl could be detected in the corresponding 15-minute fraction. It is important to note that in these cases neutral red was always present in the gastric juice.

In 5 of the 11 cases where no HCl could be detected but the acid form of the neutral red was present in the gastric juice, it may be stated with great probability that a minimal production of acid did occur, but this tiny quantity was not enough to lower the pH of the whole 15-minute fraction below 3. The lowering of the pH to 3,5, 3,75, 3,70, 3,2 and 4,6 resp. could hardly be explained but with HCl production. In further 3 cases we supposed a minimal HCl secretion (lowest pH values: 5,3; 5,5 and 5,7).

While the neutral red appeared in the normacid subjects after about 8-30 minutes (average 15 minutes), the same process took in the subacid patients 15-75 minutes (average 37 minutes) and in the achlorhydric patients 10-75 minutes (average 38 minutes). The values of the subacid and achlorhydric groups are hence practically the same. If in the achlorhydric group the appearance time of neutral red is separately analysed for patients secreting HCl after 2 and 3 mg of histamine, then the average of the former is 29 minutes and that of the latter 46 minutes. Two patients of the subacid and one of the achlorhydric group excreted the neutral red faster than the average of the normacid group.

Conclusions

Several important data were furnished by experimental investigations performed in the last years to clarify the problem of the mechanism of neutral red excretion. The process may be seen distinctly in spite of the controversy of previous publications. It seems namely an established fact that *the excretion of neutral red is not the result of a cellular activity but of passive transfer.* As to the mechanism of this transfer HÖBER (1947) presented the following theory:

In neutral media such as blood neutral red is a non-dissociated molecule, which owing to its lipoid solubility may penetrate through cell membranes and thus get in or out of the cells, including the cells of the gastric glands. In acid milieu, however, the dye becomes dissociated losing hereby its lipoid solubility. The extent of dissociation depends on the pH and a constant dissociation factor is characteristic of each dissociable molecule. Excretion of neutral red through the stomach proceeds from the serum into the cells of the gastric mucosa and from there into the gastric juice. Here a low pH prevails and dissociation of the neutral red molecules takes place. As the ions dissociated are no longer lipoid-soluble, the cellular wall becomes impermeable to them. So neutral red already ionized can no longer re-enter the mucosa and thus concentrations many times higher than those in the serum may develop in the gastric juice. Meanwhile to equalize the concentration gradient of the non-dissociated dye molecules new neutral red enters the gastric juice, where it will be ionized increasing the number of dissociated dye molecules.

RAY and YOUNG (1951) determined the ionisation constant of neutral red and established therefrom that the ratio of the dye concentration in blood to that in gastric juice is 1 : 26,5 i. e. the neutral red can reach at pH 1 a twenty-six fold concentration of that in the serum. This is the reason why the dye can easily be detected in the acidic gastric juice. In alkaline or neutral body fluids (bile, urine) the appearance of the dye is the result of either a passive filtration (urine) or active secretion (bile).

JÁVOR's experiments (1956) contributed a great deal to the understanding of the mechanism of neutral red excretion. He could prove in dogs that the secretion of neutral red is not a privilege of the parietal cells as the dye could be demonstrated even in an isolated pyloric pouch if HCl was put in it before the neutral red injection. This signifies that the decisive factor of the neutral red excretion is the pH-difference between the blood and the gastric contents. Indeed if strong alkali and neutral red were put together into the gastric pouch, absorption of the dye occured *from* the stomach. These experiments strongly support the view of HÖBER discussed above concerning the passive transfer of neutral red. BILSKI and OBRINK (1959) came to the same conclusions working with the dye, neutral-violet.

It is easily understandable, therefore, that *neutral red is excreted only if the stomach contains HCl either through the activity of the parietal cells* (e. g. after histamine) *or through acid intake from outside* (instillation). The fact that neutral red may be brought through the mucosa with the aid of acid instillation sometimes in cases of histamine refractory achlorhydria (even in several patients with anaemia perniciosa), strongly supports the view that the dye excretion is not bound to the functional integrity of the parietal cells. In pernicious anaemia an extensive destruction of the parietal cells must be supposed which renders highly improbable that the elevated concentration of neutral red in the instillate would arise through parietal cell activity. In our material in 4 out of 19 pernicious anaemia patients

the acid instillation test was positive indicating quantitative differences as to the intensity of mucosal destruction.

As the appearance of neutral red is bound to the presence of HCl, in clinical practice the dye excretion may nevertheless be considered as an indicator of the activity of parietal cells, because only these elements can produce the necessary acid. Accordingly, *the appearence of neutral red always means a simultaneous HCl secretion as well.*

Neutral red injections given together with the augmented dose of histamine highly facilitate the separation of pseudo-achlorhydria from the true. As mentioned above the appearence of the acid form of the dye means, practically always, the presence of HCl in the gastric juice. This acid may have been secreted only for a short period and in a tiny quantity and so we are not able to demonstrate it in the 15 minute-fraction. It is important to remark, therefore, *that the positive neutral red test proves that some acid production takes place even if HCl is not detectable any more.*

While the appearance of neutral red after histamine injection always means a more or less preserved acid-producing capacity, *the acid instillation test* does not inform us about HCl secretion but *gives an account of the state of a functioning glandular mass.* The positivity of the acid instillation test — even when a substantial dose of histamine is unable to bring forth acid production or to give rise to dye transfer — is, in our view, evidence of a seriously damaged mucosa, of which certain potent glandular elements still exist. Naturally these cellular remnants are not parietal cells.

The negativity of acid instillation test is even of greater diagnostic significance. The negative acid instillation test represents a serious lesion of the gastric mucosa; it means that the total mass of intact glandular cells has fallen below a certain limit: the *„neutral red threshold"*. This phenomenon occurs when there is atrophy of the gastric mucosa. Parallelly with mucosal destruction, namely, a decrease of the capillary bed takes place; as the volume of the blood flowing through the mucosa decreases, the amount of dye transferred diminishes equally. Indeed there was neither acid secretion nor neutral red excretion in any of our 25 patients with negative acid instillation test even after high doses of histamine.

Different procedures may be used to demonstrate atrophy of the gastric mucosa. On gastroscopy the diagnosis of atrophy is based on visual impressions. The radiologist draws his conclusions in favor of atrophy from the loss of rugal pattern. The deficient absorption of vitamin B_{12} suggests also atrophic mucosa even without considerable haematologic abnormalities. On gastric biopsy histologic examination reveals the deficiency of glandular elements. In our opinion to all these criteria the disappearance of glandular cells demonstrated by the acid instillation test, the *„neutral red atrophy"* may be reasonably added. The evidence furnished by this procedure is also an indirect one, nevertheless it may be more exact than biopsy, inasmuch as it enables us to obtain a picture of the whole glandular mass of the stomach whereas biopsy informs us about the histologic structure of a limited area only. In case of patchy atrophy this may lead to misinterpretations. It seems indicated, therefore, to introduce into the diagnostical procedures of gastric atrophy the acid instillation test after neutral red injection.

VI. ENZYME PRODUCTION OF THE STOMACH

The mechanism of enzyme production

The stomach produces nearly exclusively proteolytic enzymes; the small amount of gastric lipase does not seem to possess any practical importance. Organs of the enzyme production are the chief cells of the glands. In the chief cells the enzyme is present in the form of a precursor, i. e., in the zymogen granules. During secretion the zymogen granules are emptied, they appear again during the resting stage. The demonstration of this secretory cycle of the gastric enzymes was first done by HEIDENHAIN (1868). The intracellular migration of the zymogen granules in the pancreas of a living animal was described by KÜHNE and LEA (1882).

The schematic idea about enzyme secretion based on experiments of HEIDENHAIN (1875), KÜHNE and LEA (1867) and LANGLEY (1880-82) is the following. The enzyme-precursor represented by the zymogen granules in the chief cellt is transformed in the presence of gastric HCl to active enzyme, pepsin, through an autocatalytic reaction. Pepsin and pepsinogen could be produced in crystalline form by NORTHROP (1929-30-31) and HERRIOT (1936). It could be established that both are proteins appearing in various crystalline forms but having nearly the same molecular weights (42 000 $\pm$ 3000 for pepsinogen, 38 000 $\pm$ 3000 for pepsin).

During enzyme secretion secretory granules are slowly migrating towards the lumen of the glands; this progression does not cease entirely even in the resting stage Enzyme production does not need much fluid; that is why the beginning acid secretion (e. g. after histamine) is so abundant in enzyme; it simply „washes out" the enzyme content of the tubuli. In the gastric glands parietal cells are situated in the periphery, chief cells and mucoid cells more centrally which renders possible for the watery parietal secretion to wash out the thick products of the other two glandular components.

It is very difficult experimentally to get isolated secretion of some of the cell groups in spite of the fact that parietal resp. chief and mucoid cells are not stimulated through indentical pathways. It is easy to imaginate that the secretion of the parietal cells lying at the periphery must be mixed — even in case of special stimulation (histamine) — with that of the more centrally situated glandular cells. On the other hand it is dificult to obtain a pure secretion of the chief cells because of its viscosity and thickness.

Enzyme production is stimulated by vagal excitation. This gastric juice has a high enzyme, mucus and acid content. Pilocarpine is an especially strong stimulant of enzyme secretion. The relation between the hypophysis and the pepsin production is demonstrated by the experimental fact that hypophysectomy results in thé involution of the chief cells with subsequent decrease in pepsin production (BAKER and ABRAMS 1954, DEBRAY et al. 1958).

Until the last few years only pepsin was thought to be important among the proteolytic enzymes of the gastric juice. When speaking about gastric proteolysis, everyone meant the effect of peptic activity.

Gastric rennin (synonymes: rennet, parachymosin, chymase, milk-curdling enzyme) has a practical importance only in infancy. Rennin when added to milk splits the soluble casein (caseinogen) into a proteose-like substance and paracasein. The latter undergoes peptic digestion in the usual manner. The optimum pH for its action is between 6 and 6,5 and it is quite inactive at the pH of the gastric content of the normal adult. In the infant, however, the gastric pH is around the optimum (5-6,5) for the action of this enzyme. According to some observers it is absent from adult human gastric juice, here the milk-curdling effect is entirely due to pepsin. PAVLOV (1902) maintains that in the adult rennin is identical with pepsin.

The optimum pH of pepsin depends on the protein to be digested; for the casein and haemoglobin it is, e. g., 1,8, for the gelatin 2,2. Pepsin is a proteinase i. e. an enzyme which attacks the whole protein molecule by breaking its peptide linkages. Peptic digestion of protein does not go beyond the pepton stage. The action of pepsin is reversible; synthesis of protein by pepsin is also possible from a concentrated peptic digest of albumin.

The cathepsin problem.

The attack agains the „tyranny" of pepsin was based on clinical experience. In children a normal gastric proteolysis could be observed in spite of the lack of an acidic milieu necessary to peptic activity. There is some preteolysis in the achlorhydric gastric juice as well which could not again be explained by peptic activity.

The possibility was raised that this proteolysis would be achieved be the trypsin regurgitated. The optimum pH for trypsin (pH 7-8) cannot be demonstrated but in a few cases; in the others pH conditions in the stomach (pH 4-5) do not favour a tryptic activity.

FREUDENBERG and BUCHS (1940) made an attempt to bridge over „the abyss" between the pepsin and trypsin in the gastric proteolytic spectrum describing an enzyme in the gastric juice, the cathepsin. In the child's stomach according to FREUDENBERG (1941) proteolysis begins with the activity of cathepsin, the pepsin coming into action only when a suitable pH milieu is assured by HCl production. LEHMACHER et al (1950—51) even maintain that the digestion of milk in the new-born child takes place also with the aid of cathepsin.

The expression „gastric cathepsin" derives from WILLSTATTER and BAMANN (1929) who succeeded in producing out of the gastric mucosa a proteinase similar to cathepsin isolated from various organs, which was active in weak acid milieu. They thought the enzyme to represent a cellular ferment which plays a role in the protein metabolism of the cell. In the gastric juice they were unable to detect the enzyme. Earlier a cathepsinlike enzyme was already described by Japanese authors (TAKEMURA 1909, HIROYAMA 1910) but their communications were forgotten.

The widespread investigations of FREUDENBERG and BUCHS (1940) caused the question about gastric cathepsin to become a much discussed problem of medical literature. In the presence of food the pH of the gastric content ranges mostly from 3 to 6, a surrounding which is not favorable for peptic digestion, as peptic activity is decreased to one tenth of optimal at pH 3 (BUCHS 1949). That is why it was supposed earlier that the stomach acts only as a reservoir for food and essential proteolysis does not begin but in the lower parts of the gastrointestinal tract. BUCHS (1949)

emphasizes that the presence of cathepsin may already be detected by careful analysis of the original peptic activity curves of the first describers (RONA and KLEINMANN 1924). He could demonstrate the cathepsin in the mucosa in form of zymogen granules which are transformed into active cathepsin by acidification. The optimum pH range of the transformation is between pH 2,5 to 4. The transformed cathepsin is alkalisensitive but not the zymogen granules; this alkalisensitivity is greater than that of the pepsin (MILHAUD and EPINEY 1951). The optimum pH for the digestion depends on the quality of the substrate (SPRINGER 1950).

According to BUCHS (1949) cathepsin is not a second proteolytic enzyme of the gastric juice but only part of a uniform gastric protease (pepsin-cathepsin-parachymosin). This notion would be supported by the experience that pepsin and cathepsin show parallel quantitative changes (SUNDBERG 1952). Their view is shared by MILHAUD and EPINEY (1951) who use the designation of pepsin II for cathepsin. On the contrary MERTEN et al. (1952) by reason of electrophoretic analysis stoutly take a stand for the independency of cathepsin. They succeeded in isolating from gastric mucosa two enzymes, the first showing peptic activity without catheptic; the second having a predominant catheptic activity but here a certain peptic effect may be demonstrable as well. On the base of their electrophoretic investigations NORPOTH et al. (1953) are of the same opinion. CREBOLDER et al. (1951), TOLCKMITT (1954), CHRISTENSEN (1955), TAYLOR (1959), however, are definitely against the supposition of a second enzyme in the gastric juice. Perhaps it could be still mentioned that FOX (1949) describes the presence of a protease in the gastric juice which is active at pH 7,4; it is not identical with trypsin but is in connection with the intrinsic factor.

The modern concept of gastric proteolysis

Based on literary data and on our own experiments described later we are of the opinion that *some protein digestion does occur even beyond the activity zone of pepsin and within the pH milieu of the (regurgitated) trypsin.* This effect may be called catheptic activity. The question remains, however, still open whether this cathepsin represents an independent enzyme or is only part of the gastric protease.

It seems settled that even in normal stomachs digestion is started by cathepsin and peptic activity can be detected only after the development of a corresponding acidic milieu; hence the clinical importance attached to the investigation of the gastric cathepsin. It is especially important in the cases of achlorhydric or subacid gastric juices in which — together with the regurgitated trypsin — this catheptic activity represents, so to say, the only proteolytic possibility for gastric digestion.

The clinical investigation of enzymatic conditions was always pushed into the background by problems of gastric HCl secretion. The analysis of gastric HCl production is more easily practicable and seems to furnish more useful information about the state of the gastric mucosa.

The mechanism of gastric enzyme and HCl secretion as well as the stimuli whereby these two products of the mucosa are stimulated were already mentioned earlier. It is a well known fact that the absence of pepsin is a far more infrequent condition than that of HCl. In all probability this can be explained by the greater resistance of the chief cells against damaging noxa. That is why the disappearance of enzyme production is a more conclusive, although less sensitive, sign of mucosal damage. MILHAUD and EPINEY (1951) distinguish two sorts of apepsia: the so called *primary apepsia* where no enzyme is produced and a *secondary one* where the pepsin secreted is inactivated in the gastric juice having a high pH. According to our investigations the second

part of the definition is somewhat imperfect. If enzyme determinations are made rather quickly gastric ferments do not become inactivated in the majority of achlorhydric stomachs. We succeeded in demonstrating peptic activity in a good part of our achlorhydric patiens in spite of the fact that pH conditions were rather unfavorable. It cannot be denied, however, that in the gastric juices mentioned *in vivo* peptic or even catheptic activity would not be possible except in traces. We were able to demonstrate the enzyme activity by creating artificially the optimum pH conditions required. We think reasonable, therefore, to use the name of absolute apepsia for the absence of pepsin production and that of relative (or actual) apepsia for the condition where no enzyme activity prevails owing to the unfavorable gastric pH milieu. Absolute apepsia always means a serious mucosal lesion (HENNING 1934).

DELHOUGNE (1929) states that the lowering of peptic activity is a good indicator of mucosal damage; in cases of functional achlorhydrics some pepsin is always present.

BECKER (1934) maintains that complete (histamine refractory) achlorhydries are always followed by apepsia. This concept can be only partly accepted. In the majority of pernicious anaemia patients and in some achlorhydric persons (mostly those having gastric carcinoma) indeed not only lack of acid but also that of enzyme may be found. In all other cases of anacidity, however, enzymatic activity — sometimes significantly reduced — may be detected.

Pepsin secretion is higher in men than in women and, similarly to acid secretion, there is also a successive decrease with ageing (OSTERBERG et al. 1936). JANOVITZ and HOLLANDER (1952) described a linear correlation between the quantity of acid and pepsin secreted. This correlation does not seem to be a regular one as one may find considerable peptic activity in gastric juices containing no acid (OSTERBERG et al. 1936, BENGT. 1938, GLASS et al. 1950, MERTEN 1950/51, MILHAUD and EPINEY 1951). The quantity of pepsin is increased in cases of duodenal ulcer (CHINN et al. 1951, VARRÓ et al. 1951, NOVASZEL et al. 1954).

Proteolysis in the achlorhydric stomach

There are divergent opinions as to the proteolytic capacity of the achlorhydric stomach. ELSOM et al. (1942) are of the opinion that in the whole gastrointestinal tract the most intensive protein digestion occurs in the stomach and in anacidity the gastric proteolysis is strongly reduced. With the aid of intubation they managed to place into various segments of the gastrointestinal tract given quantities of protein determining thereby the digestive capacity of that same region. BRUMMER and YLI-POHJA (1954) measured the blood glycin concentration after gelatine ingestion. No definite differences were observed in test persons with and without achlorhydria.

In achlorhidry BRAMSTEDT (1953) distinguishes two sorts of gastric proteolysis. In the first case there is enzyme production without that of HCl. In these subjects the effect of cathepsin and or trypsin may be observed singularly or simultaneously (Mischproteolyse) according to actual pH conditions. In the second case there is no gastric enzyme production whatsoever as a result of mucosal atrophy; then only trypsin may be accounted for the gastric protein digestion.

The protein digestion occurring after subtotal gastrectomy represents a special problem. If no considerable mucosal damage (serious forms of gastritis, extensive carcinomatous infiltration) existed before operation, then the ferment production of the stump is sufficient for a satisfactory protein digestion as demonstrated by LINDENSCHMIDT et al. (1953) and PFISTERER (1955). This proteolysis occurs mostly in the catheptic pH-range but sometimes the trypsin may play a role too. It is highly

probable that besides the cathepsin secreted by the gastric glands the cellular cathepsin, too, which is released from the digested leukocytes and desquamated mucosal cells may help the digestion especially in anacidity (MAHLO 1953). LINDENSCHMIDT and BRAMSTEDT (1954) stoutly maintain that the optimal enzyme substitution in gasrectomized patients may be achieved by pancreas ferment preparations.

The trypsin may result in a moderate proteolysis even after total gastrectomy although the good effect of enzyme substitution is striking in these cases (LINDENSCHMIDT et al. 1953). In this connection the attention has to be drawn to the fact that some animals cannot survive total gastrectomy. But man does. One reason may be that for man the mechanical, physico-chemical preparation of food is made already in the kitchen whereas animals always eat raw food. The preparative work can be increased by dietetic measures (KATSCH and PICKERT 1953).

Our own investigations concerning gastric enzyme production

On the basis of our own experience we tried to answer the following questions:

a) Is enzyme production a more sensitive function of the gastric mucosa than the HCl secretion?

b) Is the pepsin determination a suitable method to differentiate between functional and organic achlorhydria?

c) Is the catheptic and tryptic activity of importance for the proteolysis in the anacid stomach?

ad a) In the majority of our achlorhydric cases the precence of gastric enzymes (pepsin, cathepsin) could be ascertained. In 61 patients out of 75 the dose of histamine, which was not sufficient for HCl production, resulted in evoking gastric secretion containing enzymes. In 14 cases no enzyme could be detected in the achlorhydric gastric contents. In 2 cases using higher histamine doses, simultaneously with the appearance of acid, enzymatic activity also became demonstrable. *Not a single case could be revealed where — using no matter how much histamine — the gastric juice contained HCl but no enzyme.* Quantitative data of the enzyme concentration in various secretory groups are presented in Figure 7.

Taking into consideration that in achlorhydric subjects not only the pepsin concentration but the absolute quantity of the gastric juice produced is diminished, the total quantity of pepsin is significantly decreased compared to that of subacid or normacid persons.

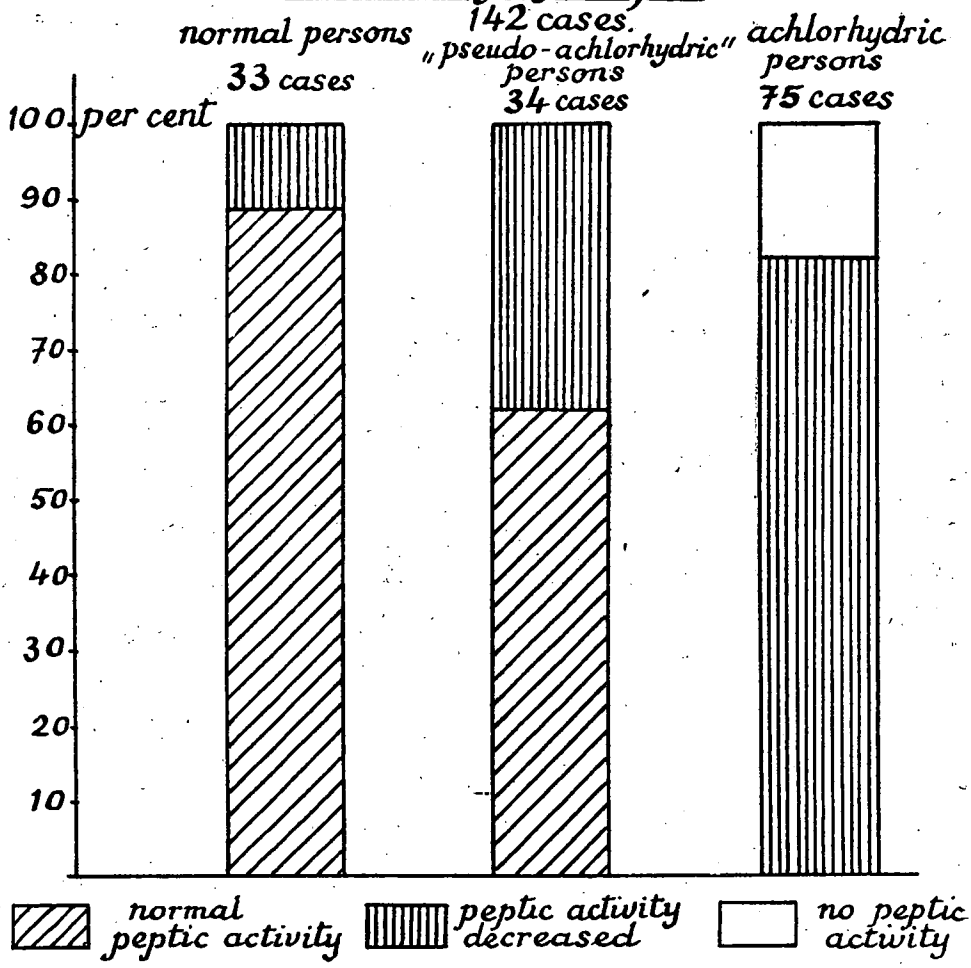
The analysis of those cases where HCl was produced only after using 3 or 4 mg of histamine and where no acid appeared even after 3 or 4 mg of histamine is especially instructive (Table 7).

It could be established that in 9 cases out of 15 without acid secretion even after 3-4 mg of histamine, enzyme production — scanty as it may be — could be detected. Out of 8 cases, where only augmented histamine doses resulted in acid secretion 7 showed the presence of enzymatic activity: in one case no enzyme determinations were made during the augmented histamine test.

The above data clearly demonstrate *that the loss of the acid-producing capacity does not involve the simultaneous disappearance of enzymatic activity.* Patients found achlorhydric after high doses of histamine retain their ability to produce gastric enzymes. The reverse case i. e. preserved acid-producing capacity with no enzyme production did not occur in our material. Even in some anaemia perniciosa patients a definite enzyme activity could be observed.

Figure 7.

Gastric peptic activity in various secretory groups.



Our experience supports the idea that *HCl secretion is a more sensitive function of the gastric mucosa than enzyme production.* Gastric glands which are already unable to produce HCl may secrete gastric enzyme (pepsin and or cathepsin) in sufficient quantity. Naturally under such circumstances the pepsin produced does not posses any practical importance as without suitable acidic millieu it must remain ineffective. We have sometimes to reckon, however, with the effect of cathepsin

Table 7.

Enzyme production and the augmented histamine test.

No acid after 3 mg of histamine				HCl secretion after 3 mg of histamine			
	Name	peptic activity mg tyrosine/ml	remarks		Name	peptic activity mg tyrosine/ml	remarks
1.	M. T. ♀	23,7		1.	E. V. ♂	43,2	
2.	P. P. ♂	15,0		2.	K. R. ♂	5,4	
3.	D. K. ♀	ø		3.	M. Sz. ♂	6,3	
4.	F. M. ♂	2,9		4.	J. L. ♂	7,7	
5.	J. J. ♀	ø		5.	Gy. K. ♀	6,4	
6.	M. K. ♀	ø		6.	J. H ♂	17,2	
7.	J. B. ♀	ø		7.	J. Sz. ♂	ø	
8.	I. Sz. ♂	2,5		8.	M. J. ♂	4,6	
9.	F. H. ♀	1,7					
10.	L. T. ♂	5,6	cathepic activity				
11.	V. Ty. ♂	ø	No acid even after 4 mg of histamine				
12.	E. T. ♀	ø					
13.	G. S ♀	2,7					
14.	V. B. ♀	4,4					
15.	A. T. ♀	4,6					

even in anacid gastric juices, although pH conditions are unfavorable in most cases even for cathepsin.

The secretory capacity of the stomach does not seem to be the same for its various products. Our experience supports those of KALK (1935) who states that acid production must be considered the most sensitive function of the gastric mucosa, it is followed by enzyme secretion and the least sensitive appears to be the fluid secretion.

A considerable mucosal damage must be supposed in the stomach which is not able to produce any enzyme; the most serious situation exists in the so called „dry achylias" where also fluid secretion is abolished or considerably reduced. *For practical reasons determinations are of value to differentiate between a more or less extensive mucosal lesion.*

ad b) One may assume that enzyme determinations may be used for differentiating between organic and functional achlorhydry. One has, however, to judge in this question with great precaution. We have already demonstrated that even in about two-thirds of the patients found achlorhydric with the augmented histamine test, enzyme activity could be demonstrated (Table 7). It is difficult to qualify these cases as pseudo-achlorhydryc for the very reason that 7 patients with anaemia perniciosa may be found among them. This clearly demonstrates that *the integrity of enzyme secretion does not exclude the possibility of an organic achlorhydry.* It must be noted, however, that in our opinion achlorhydry represents a quantitative concept and thus even complete achlorhydry does not invariably mean total lack of parietal cells, but only their decrease under a certain threshold value. Sufficient quantity of enzyme might still be produced while the number of parietal cells is already diminished under this threshold value. Lack of any enzymatic activity in the gastric juice indicates — in our view — serious forms of mucosal lesion.

Summarizing we may state that *the presence of enzyme activity does not necessarily mean the preservation of HCl producing capacity. The absence of enzyme secretion, however, — especially after large doses of histamine —, refers to serious lesion of the gastric mucosa.*

ad c) We are of the opinion that the enzyme, cathepsin, may play a part in gastric proteolysis. In gastric juices with scanty acid content one may observe even during test meals such pH ranges where catheptic activity may prevail. This situation is even more conceivable during eating. Catheptic activity seems to have importance for the physiological digestion independently of the fact whether we consider it as a special enzyme or part of the homogeneous gastric-enzyme-complex.

In achlorhydric patients besides cathepsin also the tryptic activity reaching the stomach through duodenal regurgitation may have some importance. We also hold the view that the two enzymes act simultaneously and successively (BRAMSTEDT-Mischproteolyse). Our experience demonstrates that duodenal regurgitation using the same aspiration technique is more common in anacid patients than in persons having more or less HCl production. The appearance of acid obviously through reflexes results in the cessation of duodenal regurgitation.

Data of the demonstrability of tryptic activity are shown in Table 8.

Table 8.

Values of tryptic activity of the gastric juice.

	Total number of cases	Cases where tryptic activity was demonstrable
Achlorhydric group	38	25
Subacid group	22	9
Normal group	22	7

SECTION III

Clinical studies

VII. ANAMNESIS AND COMPLAINTS OF ACHLORHYDRIC SUBJECTS

A review of the literary data

The stomach of healthy persons reacts to adequate stimuli with HCl production so *achlorhydry must be considered from a physiological point of view anyhow as a pathological state.* It is another problem whether the incapacity of the stomach to produce acid should be regarded as a disorder with symptoms which needs special treatment.

Some authors consider the achlorhydry to represent a „sea of complaints". When one does, however, critically analyse the true relation between the complaints and the lack of gastric acid secretion, in most cases this cannot be verified. In such cases the complaints are obviously not caused by the achlorhydry but by other pathological events which result also in anacidity or which are quite independent of the gastric secretory anomaly; sometimes the symptoms are of psychic origin. *The majority of achlorhydric persons have no digestive complaints whatsoever.* In these cases the lack of acidity is revealed when performing a routine or experimental gastric analysis during a general check-up of the patient.

In the chapters dealing with achlorhydry of the current medical handbooks nearly all epigastric symptoms are enumerated as possible findings in anacid persons. The epigastric (mostly postprandial) pain (achylia dolorosa), the heartburn, the so called dyspeptic complaints and the diarrhoea are especially emphasized. Dyspepsia would mean ill defined complaints which are in connection with meal or are thought to be so. It mostly consists of nausea, bad taste in the mouth, malaise, lack of appetite and coated tongue. Finding no organic explication of the above symptoms the lack of gastric acid during a routine test meal helps the examiner to find a „diagnosis" (deus ex machina!).

Some of the complaints are consequences of a disease resulting in anacidity as well. Thus the complaints of patients with chronic gastritis, cholecystitis, enteritis, hepatitis, pancreatitis and gastric carcinoma are caused in all probability by these diseases. How these ailments effect gastric acid secretion is not yet cleared, but their inhibitory influence seems to be established.

Sometimes after healing of the illness the symptoms disappear entirely but the anacidity remains which also proves the independency of the complaints of secretory conditions.

A good part of complaints in achlorhydria does not refer to the stomach but is of nervous character: so headache, neuralgia, salivation, lack of appetite, malaise. These neurotic complaints are only insofar in connection with the achlorhydry that mental depression may cause a decrease of gastric secretion through central mechanisms. Chronic fatigue was a chief complaint in 36 out of 100 achlorhydric patients as

published by EGGLESTON (1931). Atrophy of the tongue was described which resembled that of old men. Some even maintain that the diagnosis of gastric acid deficiency may be established by only looking at the tongue without performing gastric analysis; this is, however, a strong exaggeration. Among the complaints one frequently encounters „water vomiting" or „water belching"; this fluid is entirely tasteless or sometimes salty or bitter but never acidic. It is not a specific symptom as one may find it even in superacid persons; perhaps it is due to the increased „diluting secretion".

According to SCHMIDT (1932b) hunger pain is a frequent complaint. The postprandial distress is better suspended by moving than by rest; this is contrary to the behaviour of the ulcer pain. NYMAN (1932) emphasizes the periodic nature and long duration of the achlorhydric complaints. He maintains that the pain is mostly postprandial with epigastric localisation. In about 6 per cent of his patients there was hunger pain which disappeared after eating. Fatty meals occured in a striking frequency (about 98 per cent) among the causes which preceded the appearance of the symptom. BLOOMFIELD and POLLAND (1935) followed with attention the fate of 45 histamine refractory achlorhydric persons where the absence of gastric acid was detected by a routine test meal; in contrast to aforementioned authors they observed no gastric complaints. During an observation period of one to seven years no gastric carcinoma or pernicious anaemia developed in these patients; one of them even regained the ability to produce gastric acid. Also BOCKUS et al. (1932) are of the opinion that anacidity can be observed more frequently in persons without digestive complaints. HETÉNYI (1940) directs attention to the great number of symptomless subjects with gastric achylia.

In this respect BRUMMER's (1947) interesting investigations are worthy of mention. He performed a routine gastric analysis in all persons entering the Clinic independently of the fact whether or not they had digestive complaints. Analyzing a substantial material (364 patients) he could ascertain that the frequency of dyspepsia is nearly identical in patients with achlorhydria (insulin refractory) or with normal levels of acidity (16 resp. 18 per cent). He compared the complaints of 50-50 dyspeptic persons with and without gastric HCl secretion and found no significant or characteristic difference as to the nature of the symptoms. According to him the experience that the frequency of gastric acid deficiency increases with aging, while dyspeptic distress is the most common in the thirties after which it gradually becomes less and less, speaks against a causal inherency.

The problem of diarrhoea in achlorhydrics, the so called „gastrogenous diarrhoea" merits special interest. Ever since this diagnosis was first mentioned by EINHORN (1896) and OPLER (1896), gastrogenous diarrhoea has always been amply discussed in medical handbooks; its independence seems to be an established fact. ALLODI (1935) e. g. insists upon gastric acid deficiency playing a decisive role in the appearence of gastrogenous diarrhoea. BOCKUS (1944) maintains that „gastrogenous diarrhoea almost invariably responds to acid therapy".

This opinion is perhaps based on the assumption that only those diarrhoeas may be considered gastrogenous which stop after HCl administration. If it remains unchanged, the diarrhoea is not gastrogenous.

In SCHÜTZ's (1922) material the frequency of the diarrhoea is about 9 per cent between anacid persons. STRASSER (1928) after reviewing the data of several authors estimates the frequency of achylic diarrhoes to 15-30 per cent. In WILKINSON and OLIVER's (1931) view the chief characteristic of the gastrogenous diarrhoea is that

it can be abolished by small doses of HCl. Besides the diarhoea flatulency, depression, coated tongue and diverse neurotic complaints can often be observed. Among the 104 anacid patients of BRINCK and WICHELS (1933) about one-third were inclined (sic!) to diarrhoea.

It cannot be denied that one may encounter cases of diarrhoea in achlorhydric persons and that some diarrhoeas (in HETÉNYI's [1951] view about 10 per cent) disappear after HCl administration. But the fact itself that not *all* achlorhydrias are accompanied by diarrhoea and that a great part of the diarrhoeas in achlorhydric persons are *not* influenced by HCl speaks against gastric acid deficiency being the exclusive factor. Diarrhoea is not a very frequent symptom in achlorhydria. By no means can it be considered as a characteristic feature of the achlorhydric condition because constipation occurs at least just as often. Among the 100 anacid patients of EGGLESTON (1931) 14 had normal stools, 75 had constipation, 8 had diarrhoea and 3 had diarrhoea alternating with constipation. Even among the anacid patients of BOCKUS et al. (1932) chronic constipation occurred more often than diarrhoea. In SWINNERTON and TANNER's (1954) anacid (not histamine refractory!) material constipation could be observed 3 to 4 times more frequently than diarrhoea. Among RAPPAPORT's (1955) achlorhydric patients 38 had constipation and only 13 diarrhoea. The diarrhoea was not influenced by HCl but in one patient; HCl exerted no effect on constipation.

It was GUTZEIT (1933) who emphasized how often we speak of gastritis although in reality a gastroenteritis is present in most cases. So BRINCK and WICHELS (1933) consider the simultaneously existing enteritis to represent the causative factor in achylic diarrhoea. They think that disturbances of intestinal function create favorable circumstances for an upward migration of the flora of the lower intestinal segments. The symptoms depend on the predominance of gastritis (gastric complaints) or enteritis (diarrhoea). BITTORF (1914) explains gastrogenous diarrhoea by the inflammation of the caecum and colon ascendens; he found hypermotility in these regions by fluoroscopy. Only 2 per cent of the achlorhydric patients of DOMINICI and FURBETTA (1953) (excluding those with anaemia perniciosa) complained of diarrhoea. They do not think that the diarrhoea would be directly caused by the acid deficiency, but rather by a concomitant enteritis. In their cases the diarrhoea did not stop after HCl therapy.

In our previous work (SCOSSA et al. 1955) we emphasized that gastrogenous diarrhoea is a much more infrequent condition than generally thought. While studying chronic enteritis and nutritive allergy we repeatedly met patients who had achlorhydry and diarrhoea. These diarrhoeas could not be settled with HCl therapy, but only with the elimination of the allergen or with codein medication, which proved that they were not of gastrogenous origin, but diarrhoeas due to nutritive allergy or chronic entiritis in an achlorhydric person. We succeeded in demonstrating that the stool in diarrhoea of nutritive allergy does not become acidic in case the patient has no gastric acid, though otherwise this is quite a regular phenomenon. At the time of the allergic reaction namely a large quantity of unbuffered acidic gastric content suddenly plumps into the intestines causing mass peristalsis and acidic diarrhoea. In achlorhydric patients with nutritive allergy the abrupt gastric emptying, the peristalsis and the diarrhoea similarly take place, only the stool does not become acidic; this mechanism could be verified by intestinal intubation (VARRÓ et al 1955).

In our opinion *the cause of the gastrogenous (anacid) diarrhoea is not the gastritis or by no means the gastric acid deficiency but the enteritis which is simultaneously present.*

Analysis of our material

The chief complaints of our achlorhydric patients are presented in Table 9.

Table 9.

Digestive symptoms of our achlorhydric patients.

	Cases:
Without digestive complaints	61
Epigastric pain	25
Diffuse abdominal pain	25
Dyspeptic symptoms	8
Pain in the right hypochondrium	17
Heartburn	3
Total number : 61 + 78 = 139	

As demonstrated nearly half of the patients did not give account of any digestive complaints. Symptoms most frequently encountered in the anamnesis were pain felt in the right upper quadrant or diffusely in the abdomen or postprandial epigastric pain. It was surprising that „dyspeptic" distresses were mentioned in a few cases only. Typical heartburn was related by three patients having no gastric acid.

Special attention was focussed on the occurence of diarrhoea. For corresponding data see Table 10.

Table 10.

The frequency of constipation and diarrhoea in achlorhydrics.

Total number	193 patients
Diarrhoea	(34)
Diarrhoea only in the anamnesis	15
Diarrhoea alternating with constipation	7
No diarrhoea	(159)
Constipation	28

It can be seen that in about 5/6 of the cases diarrhoea could be detected neither in the anamnesis nor among the actual symptoms. In 15 out of 34 patients diarrhoea figured only in the anamnesis; actually they had normal stools. This is a characteristic feature of functional diarrhoeas. In 7 patients diarrhoea alternated with constipation; this too occurs in diarrhoea of intestinal origin and by no means fits into the clinical picture of gastrogenous diarrhoea. The final clinical diagnoses of our achlorhydric patients with diarrhoea are presented in Table 11.

Table 11

Final diagnosis of our achlorhydric patients with diarrhoea.

(34 patients)

Chronic enteritis	6
Irritable colon	6
Nutritive allergy	2
Chronic pancreatitis	1
Chronic ulcerative colitis	1
Non-tropical sprue (no diarrhoea in the remission)	2
Alkoholic polyneuritis	1
Cholangitis (coli)	1
Hyperthyreosis	1
Polyposis < gastric	1
Polyposis < intestinal	1
Acute intestinal infection	2
Nephrolithiasis	1
Pernicious anaemia (diarrhoea only in the anamnesis)	2
Origine unknown	4
Gastrogenous diarrhoea (?)	2

Most often, in 20 out of 34 cases, intestinal diseases were found as causative factors. In 4 patients the cause of the diarrhoea could not be detected; HCl administration was without effect. The possibility of the existence of a gastrogenous diarrhoea arose in 2 cases. Particulars of these cases are presented as follows:

L. O. 48 years old, male. Pernicious anaemia recently detected. Diarrhoea for 3-4 years. He has daily 3-4 stools of mushy consistency and of yellow colour; during defecation he feels loud gurglings in the lower parts of the abdomen. In his experience diarrhoeas are evoked especially by fatty meals and milk. Since the time his anacidity was discovered a year ago, he has been taking daily 2×20 drops of diluted HCl and carbo medicinalis. His other complaints are consequences of the basic disease (funicular myelosis, anaemia).

When entering the Clinic he was very anaemic and had diarrhoea. Liver therapy is begun together with HCl administration (2 × 40 drops daily). The diarrhoea ceases and the stool remains normal for a week. We omit the HCl drops. The stool remains normal for a couple of days than becomes mushy again. We reinstitute the HCl therapy but the stool remains mushy henceforward.

L. T. 58 years old, male. 38 years ago he had bacillary dysentery. For a year he has diarrhoea; he declares he has about 10 loose bowel movements daily with much pus

and mucus. These permanent diarrhoeas stopped 3 month ago as a consequence of medical tratment (?) but reappear after fatty meal or milk accompanied by abdominal distention and cramp.

After admittance he empties 4-5 loose, mildly acidic stools daily. After fasting and on basal diet (flour, fat, sugar) he has only one soft stool daily. His regimen is gradually built up; on a diet poor in fat and containing no milk and egg with 3 × 20 drops of dil. HCl he has 1-2 soft stools daily. Then we are substituting without his knowledge the HCl with citric acid. He empties again 5 mushy stools daily. The HCl is reinstituted, but the stools remain mushy although their number is somewhat decreased. We have thought the diarrhoea to be of allergic origin but the presence of a gastrogenous factor cannot be excluded.

Conclusions

On the basis of literary data and of the analysis of our own material we have come to the following conclusions:

a) *The causal relation between the digestive complaints of achlorhydric persons and the gastric acid deficiency is not conclusive.* Often one can find some disease which properly justifies the presence of the symptoms. On the other hand *the number of those persons who are entirely symptomless from the digestive point of view in spite of the achlorhydry is not at all insignificant (in our material about 44%).* The rate of symptomless achlorhydrics is undoubtedly higher in reality than in our material as the persons examined were clinical patients who were admitted to the Clinic because they had some — if not always digestive — complaints. A great number of symptomless achlorhydrics could have been found by screening examinations; here the absence of causality between the achlorhydry and the digestive symptoms would be still more conspicuous.

b) *Gastrogenous diarrhoeas* may sometimes be encountered, but anyhow they *belong to the most infrequent conditions.* In only two of our achlorhydric patients with diarrhoea did we find some connection between HCl and the cessation of the diarrhoea, but even here the relation was not indisputable. The majority of achlorhydric diarrhoeas are of intestinal origin; therapeutic efforts directed towards the intestinal disorder had generally a good effect.

c) *Achlorhydry may exist in entirely symptomless persons.* The symptoms which arise later are mostly related to other diseases of the digestive system. It is another question whether the absence of gastric acid is a promoting factor in diseases of the „chylopoetic system" (BAMBERGER) and so exerts an indirect influence on the development of digestive complaints. The problem will be discussed later.

VIII. CHRONIC GASTRITIS AND ACHLORHYDRY

The problem of chronic gastritis

Chronic gastritis is a gastric disease which arises as a consequence of various pathological events, causes divers complaints, results in abnormal changes of gastric secretion and produces alterations which may be detected by gastroscopy, radiological and histological examination. The genesis, pathological substrate, frequency of occurrence and clinical significance of chronic gastritis is a hitherto widely discussed problem. Here we shall confine ourselves exclusively to its relation to gastric acid deficiency.

The tentative diagnosis of chronic gastritis is made in cases of diffuse postprandial gastric complaints which do not cease after subsequent feeding. Clinical examinations do not show definite signs of biliary, hepatic, small intestinal or pancreatic disease and thus it may be supposed that the trouble is of gastric origin. The diagnosis seems to be confirmed by a radiological picture presenting irregular, indistinct or coarse mucosal pattern or by gastroscopy showing signs of inflammation, oedema, small haemorrhages and ulcerations. At the end gastric biopsy may furnish final evidence showing the histological picture of inflammatory reaction or glandular atrophy.

Comparative study of the results of various kinds of gastric examinations revealed, however, unexpected incongruity. In cases which were considered clinically as chronic gastritis, biopsy material did not show signs of chronic inflammation and inversely, histology furnished evidence of extensive round cell infiltration in symptomless persons (YLVISAKER et al. 1955, PETZEL and MOLL 1960). That is why a number of clinicians are reluctant to accept the diagnosis of chronic gastritis without corresponding endoscopic and bioptic findings.

Naturally there are opposite views as well. So KUCKUCK (1931) described the clinical picture of the painful, anacid corpus-gastritis. The symptoms are similar to those of ulcer disease, but a real ulcer can never be demonstrated in these patients, mostly young asthenic persons. MACHELLA (1953) stoutly maintains that the clinical features of chronic gastritis are so characteristic that the diagnosis can be made simply on the basis of the anamnestic data without using any other diagnostical resource. SERI and VALENTA (1943) are of the opinion that achlorhydry is the most typical symptom of the allergic gastritis.

According to BRINCK and WICHELS (1933) symptoms of achylia are in reality always those of an anacid gastritis. In their view the anacidity in gastritis may be either related to an actual gastritis, (then it is reversible) or the consequence of repeated gastritic processes, (this is already irreversible). SPIRO and SCHWARTZ (1958) maintain that in superficial gastritis there is blockage in the neck of the glands and

this, together with necrobiosis of the neck cells, may lead to temporary achlorhydria.

The analysis of the secretory conditions would also furnish some help to gastritis diagnosis. KATSCH (1953) describes that secretory alterations would represent highly sensitive signs of gastritis; he considers gastric analysis to be a more important tool for the diagnosis than gastroscopy or radiology. Similarly LAMBLING et al. (1953) are of the opinion that the correct evaluation of the data of gastric analysis renders a proper diagnosis of gastritis possible.

As to the correlation of gastric bioptic finding and secretory conditions we want to emphasize that the microscopical alterations seen in the tiny little piece of tissue is by no means always indicative of the histological state of the gastric mucosa. Thus it is not surprising to find reports on normacidity or superacidity in cases of atrophic gastritis (PETZEL and MOLL 1960, CHELI et al 1961) and inversely normal glandular structure in true achlorhydrias (KRENTZ and MERTEN 1961).

The stomach in chronic gastritis is rather characterized by low acidity values; superacidity indicates acute exacerbation of the inflammatory reaction. Because of progressive mucosal destruction these acute exacerbations are accompanied less and less by the superacid secretory period, ultimately a final condition the anadenia develops, where the destroyed glandular elements are no longer capable of enzyme and acid production. The process shows much similarity to the course of chronic nephritis. Here too the occasional acute exacerbations bring the kidney ever nearer and nearer to total renal insuficiency. It may be important to know, therefore, from a diagnostical point of view that the achlorhydria which develops through superacid periods to total gastric acid deficiency is usually of gastritic origin.

The more definite is the acid and enzyme deficiency, the more we must suppose an irreversible lesion of the mucosa.

In our view *the relation between the achlorhydria and the chronic gastritis is an unidirectional one. Achlorhydria may be the consequence of chronic gastritis. Achlorhydria itself, however, does not mean necessarily chronic gastritis,* because the acid deficiency may be the consequence of numerous pathological processes of which chronic gastritis must be considered as only one — and perhaps not even the most important — representative.

That is why we cannot share the opinion of LAMBLING et al. (1954) who maintain that „histamine refractory achlorhydry suggests nearly always simultaneous, serious, mostly atrophic gastritis".

The importance of gastroscopic and bioptic examinations for the study of a possible interrelation of achlorhydria and chronic gastritis

It is a great advantage of gastroscopy that the impression gained of the gastric mucosa is a direct, visual one. But the evaluation of what has been seen is not an easy task. Even such an excellent expert of gastroscopy as E. D. PALMER (1954) has to admit that, e. g., in about 80 per cent of cases diagnosed as hypertrophic gastritis the histologic examination failed to reveal inflammatory changes. A diagnostical mistake can be commited also inversely. So, e. g., SELEZNICK and KINSELLA (1953) could histologically demonstrate signs of chronic inflammation in about 60 per cent of mucosal pieces considered as normal by gastroscopy. LUNDBAEK (1949) compared the gastric complaints of persons with normal and pathological gastroscopic findings; he did not find any substantial difference. His results were confirmed by FINDLEY et al. (1949).

This divergency may be explained by a considerable plasticity of the mucous membrane. Since the observation of WOLF and WOLFF (1947) it is known that the mucosa may undergo considerable changes purely as a result of emotional factors. The typical endoscopic picture of „gastritis" may arise and disappear again in a person with normal stomach. HETÉNYI (1951) emphasized how often one can find "hypertrophic" mucosal pattern by radiology which turns to „atrophic" in a couple of days; he recommends, therefore, great caution in the radiological diagnosis of chronic gastritis.

As to the interrelation between gastroscopic gastritis and secretory conditions there is in all probability a close connection between atrophic gastritis and achlorhydry (FUNDER and WEIDEM, 1952). As a matter of fact in most cases the gastroscopist can diagnose only gastric atrophy with absolute certainty, the existence of gastritic changes may be verified only by simultanously performed biopsy (YLVISAKER et al. 1955). There are namely no symptoms pathognomic to atrophic gastritis (DAILEY et al. 1953; PALMER, 1953; HENNING et al. 1955; SIURALA, 1957) since the latter may exist also in persons without any digestive complaints (PALMER, 1953). Finally it may happen that another coexistent process may be the cause of the actual complaints.

The gastroscopic impression of an atrophic mucosa does not always necessarily mean the definite absence of acid secretion. RICKETTS et al. (1949) describe that they found anacidity only in 30 per cent of patients whose mucosa was diagnosed as atrophic on gastroscopy; the same rate was 5 per cent in persons with normal gastroscopic finding. In HENNING et al's material (1955) the rate of histamine refractory achlorhydrics was only about 40 per cent among patients with endoscopic atrophy. SCHINDLER et al. (1940 a) note that in about 5 per cent of 101 histamine refractory achlorhydrics the mucosa was gastroscopically completely normal.

STEMPIEN et al. (1953) found achlorhydry (after 0,5 mg of histamine) in about 8 per cent of patients with normal gastroscopic picture; the same rate was 38 per cent in the atrophic group; no achlorhydry was detected among patients with endoscopic hypertrophy. Sometimes acid production may be detected in a stomach the mucosa of which was found to be extremely atrophic by biopsy; this can be explained by the fact that glandular destruction is not of the same extent in various parts of the stomach, there is patchy atrophy and the biopsy may have been made from an atrophic portion (SIURALA and LEHTINEN, 1953).

Nevertheless there is a parallelism — though not absolute — between mucosal atrophy and gastric acid deficiency. It is difficult, however, to ascertain whether the existing atrophy is the result of foregoing inflammations or of other factors. So DOIG et al. (1950) performed gastric analysis in 134 healthy young men and detected one achlorhydry (after 0,5 mg of histamine) among them. In this case histology of a mucosal piece gained by biopsy showed definite atrophy without significant signs of inflammation. His haematological status was entirely normal, but there was anaemia perniciosa among the relatives.

Our own investigations

Gastroscopy was performed in 72 achlorhydric patients.

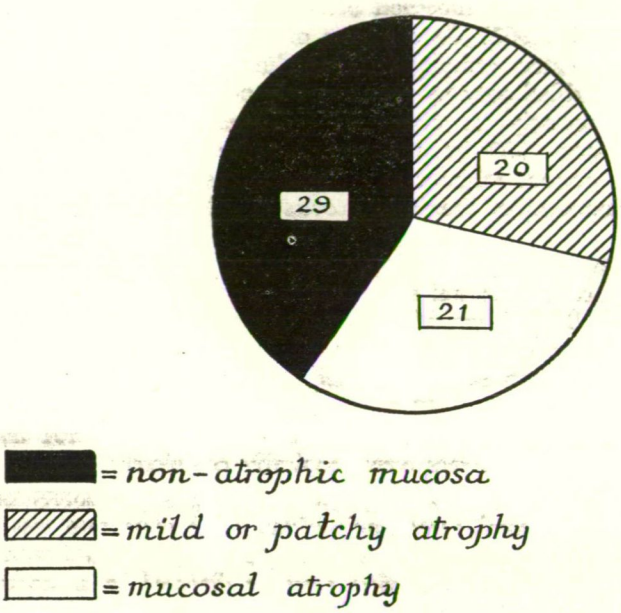
We found that achlorhydry was not always linked with mucosal atrophy (Figure 8.).

In about half of the cases no endoscopic atrophy could be seen. In this group, in 4 cases the mucosa seemed rather hypertrophic, in 2 patients a superficial gastritis

Figure 8.

Gastroscopic impression in true achlorhydrics.

70 cases.



could be diagnosed, in the remaining patients the mucosa seemed entirely normal. Definite atrophy could be observed only in about 30 per cent of the cases examined. In 20 patients the atrophy was patchy or of a mild degree.

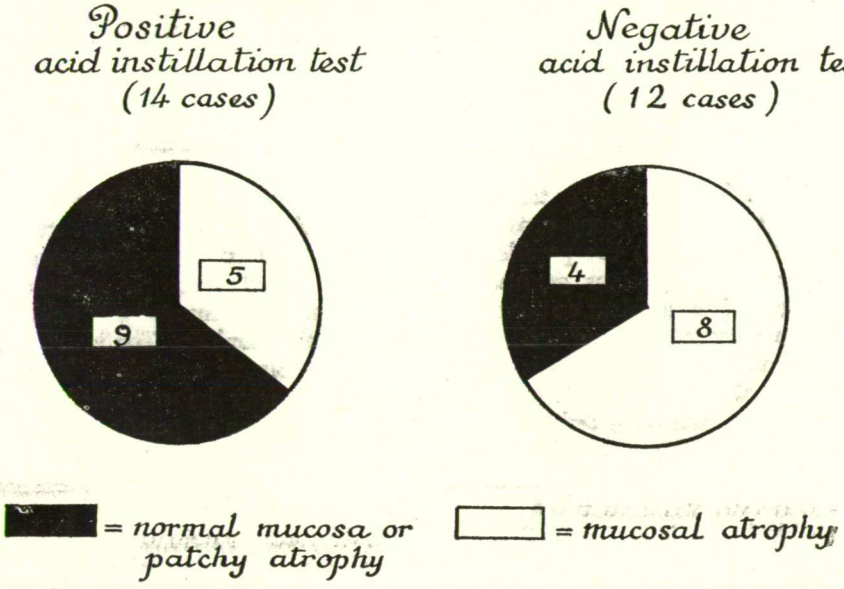
Our experience supports the findings of those investigators who gave an account of an incongruity between the gastroscopic picture and the secretory conditions.

We compared the results of the acid instillation test after neutral red injection (see page 43) with the gastroscopic findings in 26 cases (Figure 9).

In case of a positive acid instillation test (14 cases) normal musoca or patchy atrophy was found in 9 cases; in 5 patients there was definite atrophy. In case of a negativ instillation test (12 cases) definite atrophy could be seen in 8 patients while there was patchy atrophy or no atrophy at all in 4 cases.

Figure 9.

Relation between the acid instillation test and the gastroscopic finding



XI. ACHLORHYDRY AND GASTRIC CARCINOMA

It has been known a long time that there exists some interrelation between anacidity and gastric malignant growth. In early statistics since the first communication of VELDEN (1879) the parallel occurrence of these two conditions seems to be overemphasized. Physicians generally accepted as a rule that the presence of gastric carcinoma is equivalent to gastric acid deficiency and inversely if acid production can be observed, it is unjustified to suspect gastric neoplasm. The interrelation — although doubtlessly present — is far from being so simple and close. The high frequency rate of early statistics as to the parallelism may be explained by the imperfectness of the test meal technique and by late recognition of gastric carcinomas. As a result of the introduction of more accurate methods for gastric analysis and of earlier diagnosis of gastric malignancies more and more carcinomas were observed with normal or even increased acidity.

Thus achlorhydry is not an obligate symptom of gastric carcinoma especially in the initial stage. Meanwhile it cannot be denied that gastric acid deficiency occurs more frequently in carcinoma patients than in healthy persons. According to literary data about 70-80 per cent of gastric carcinoma patients do not have acid secretion. In HARTMANN's (1922) 551 carcinoma cases about 30 per cent had free HCl. COMFORT and VANZANT (1933, 1934) reported that achlorhydry can be found three times so often in gastric carcinoma patients than in normal persons. KATSCH (1953) calls attention to the fact that sometimes acid secretion fails even in cases of small gastric malignancies. In the 200 gastric carcinoma patients of KADE (1949) 69 per cent showed anacidity; suparacidity could be observed in 5 per cent. Out of DOMINICI and FURBETTA's (1953) 72 carcinoma patients two were superacid and two normacid; histamine refractory achlorhydry could be detected in 28. LEVIN et al. (1949) described that not only the acidity but also the quantity of the secretion is decreased in carcinoma patients. HITCHCOCK et al. (1955) compared in screening examinations the frequency-distribution of malignant growth in anacid, subacid and normacid persons of the same age. They reported that the frequency of carcinoma in the subsecretor group was 5,2 times greater than in the group of the normosecretors. They recommend the systematic screening of older people with anacidity.

SMITH and JORDAN (1948) found gastric acid in 40 per cent of 600 patients with gastric malignancy. In MOORE and MORTON's (1955) material the rate of persons with acid secretion was 34 per cent. Among the carcinoma patients of HÖHNE (1955) about the half (54,5%) showed histamine refractory achlorhydry, 23 per cent had no acid during a simple test meal (without using histamine) which means that 77,5 per cent belonged to the subsecretor group. In his view gastric acid deficiency represents an important diagnostic aid in detecting gastric carcinoma. NIAZI et al. (1949) described that in cases of extragastric malignancies the number of anacid per-

sons is not increased. In cases of gastric polyps or carcinomas, however, the rate of achlorhydrics was far beyond that of the normal group.

In case of gastric carcinoma achlorhydry is influenced by a number of factors, first of all by the extent of the malignancy. The less extensive are the malignant changes, the more probable is the existence of a gastric acid secretion (COMFORT, 1951). The type of the malignancy plays a role too. HEBBEL and GAVISER (1948) state that one may find acid secretion relatively often in the diffuse infiltrative form. The polypoid form on the other hand goes frequently together with anacidity. Anacidity is rather infrequent in ulcerated dishlike tumors surrounded by an elevated wall (Ringwall-Karzinom), here the rate of superacidity is relatively high, about 13 per cent (BRÜHL, 1944).

The localisation of the carcinoma has also some importance for secretory conditions. Acidity occurs most frequently in carcinomas situated in the antrum and pylorus. On the contrary, tumors in the fundus are regularly accompanied by anacidity.

If the question is raised, what is the cause of acid deficiency accompanying gastric tumors the following possibilities may be considered:

a) *Inborn mucosal defect.* The unexplainable, juvenile achlorhydries speak in favour of this theory. COMFORT et al. (1948) collected the results of gastric analyses of carcinoma patients which were made two or more years before the diagnosis of the tumor was established; they generally found a subsecretory reaction.

b) *Progressive degenerative process.* STEFANO (1940) describes a 32-year-old man who had been treated during eight years for achlorhydry, when a gastric carcinoma could be diagnosed.

c) *Chronic atrophic gastritis.* According to literary data this occurs frequently in carcinomatous stomach (GUISS and STEWART, 1943; WARREN and MEISSNER, 1944; STOUT, 1945; SCHINDLER, 1947). The statistical correlation between pernicious anaemia and gastric carcinoma is widely known, although some authors deny its reality. So WEINBERG (1951) maintains that pernicious anaemia has nothing to do with carcinoma. In pernicious anaemia a simple atrophy can be found while there exists pangastritis in gastric carcinoma, which is most intensive at the pylorus. There is no gastritis whatever in pernicious anaemia and the atrophy is most intensive in the fundus and the cardia. He is of the opinion that carcinomas in pernicious anaemia are caused by carcinogens contained in liver preparations. NIEMETZ and MEAD (1954) followed with attention 110 persons with atrophic mucosa of whom 85 had pernicious anaemia and 25 simple atrophy. Three patients of the former and one of the later group developed gastric carcinoma. MAGNUS and UNGLEY (1938) state that in pernicious anaemia achlorhydry can be explained by atrophy and a significant decrease of the parietal cells, while in carcinoma the same is caused by gastritis. GUISS and STEWART (1943) reported that the frequency of atrophic gastritis is the same in carcinoma patients and in healthy persons of the same age. The unique relation between the two conditions would be that the frequency of both atrophic gastritis and carcinoma increases with ageing.

d) *The presence of a substance inhibiting acid secretion.* This assumption would be supported by the experiments of BRUNSCHWIG (1939) mentioned earlier (see p. 36) and by the experience that sometimes even small tumours are accompanied by achlorhydry (KATSCH, 1953).

e) *Carcinoma would increase the preexisting secretory depression.* Some authors report that a preexisting subacidity turned to anacidity at the appearance of the carcinoma (ROBERTSON, 1935; SHAY and SCHLOSS, 1934).

f) *The frequency of both gastric carcinoma and of anacidity increases with ageing.* RAFSKY and WEINGARTEN (1947) succeeded in demonstrating achlorhydry in 17 per cent of symptompless persons above 65 years of age. BUGÁR-MÉSZÁROS and AUGUSZTIN (1948) found anacidity with the alcoholic test meal in about the half of old persons between 65 and 88 years without any digestive complaints. As it is well known gastric carcinoma is most frequent between 50–70 years of age, thus there exists a fair chance for statistical coincidence.

Gastric carcinoma may cause secretory depression:

a) by producing a gastritis,

b) by destructing the acid producing cells (especially in cases of fundic tumors),

c) by increasing the neutralizing component through exudation,

d) by diminishing the production of gastrin (especially in cases of antral tumors),

e) by decreasing gastric secretion through cachexy and vitamine deficiency.

Carcinoma patients with acid secretion seem to be prognostically in a better position (COMFORT, 1951). The reason may be that gastric pain is more frequent (and occurs earlier) with normal secretion than with sub- or anacidity (RIVERS and DRY, 1939).

Also gastric polyposis is frequently accompanied by anacidity. This acid deficiency is a useful sign to differentiate it from hypertrophic gastritis („giant hypertrophic gastritis").

Anacidity supports the presumptive diagnosis of gastric carcinoma or polyposis. The overestimation of anacidity as a diagnostical sign, however, may lead to serious misinterpretations as the relation is not an exclusive one.

X. ACHLORHYDRY AND SOME OTHER DISEASES OF THE DIGESTIVE SYSTEM

1. According to various statistical data anacidity occurs in 18—45 per cent of patients with *chronic hepatitis and cholecystitis* (KATSCH, 1953). This may be the result either of a concomitant gastritis or of a reflex inhibition of the secretion. LAMBLING and GOSSET (1948) state that the regurgitation of the alkaline duodenal juice would play a decisive role in the genesis of dyspeptic complaints. The alkaline juice results in a decrease of acid secretion not only through neutralisation (total acidity is also decreasing) but through some inhibitory effect the mechanism of which is not yet clarified (enterogastron?, bile acids?). In their view long-standing reflux causes achlorhydry and lasting gastritic complaints. BERGMANN (1933) maintains that through descending infection the bacterial flora of the anacid stomach plays an important role in the appearance of cholangitis. HECHTMANN (1926) is of the opinion that about 50 per cent of the cholecystitis patients are anacid, whereas BOCKUS (1944) maintains that the frequency rate of anacidity is entirely normal in cholecystitis and cholelithiasis. This latter opinion was already expressed by VANZANT et al. (1932).

From a practical point of view it is important that sometimes only the achlorhydry is detected and the complaints are attributed to the secretory deficiency, although the trouble is caused by a diseased liver or gallbladder. BERG (1925) emphasized that sometimes even entirely „silent" cholecystopathies may cause secondary anacidity.

Acute cholecystitis is accompanied rather by superacidity. Parallely with the development of chronicity the acidity values become less and less (WICHELS and BRINCK, 1933).

2. Also *chronic pancreatitis* is accompanied by lower acidity values, sometimes by anacidity. It is rather difficult to ascertain which of the two conditions was the first. The decrease of gastric secretion affects the production of pancreatic juice. MARCZEWSKI (1929) states that in achlorhydry the humoral phase of the stimulation of pancreatic secretion is lacking, only neural stimuli remain; as a consequence the quantity of pancreatic juice is significantly reduced but its enzymatic content is increased. As contrasted with him BETTONI (1935) found a normal pancreatic secretion in achylic persons. LANDAU and GLASS (1929) discovered simultaneously existing pancreatic achylia in 9 achlorhydric patients. They emphasize that the two achylias may occur also in isolation.

3. The problem is not yet settled whether there is a close connection between achlorhydry and *chronic enteritis*. According to our bacteriological investigations (see page 98) in cases of achlorhydry the duodenal flora is mostly identical with that of the stomach; thus the possibility for foreign bacteria to reach the small intestine is given and an inflammatory reaction may ensue. Achlorhydry itself, however, seems

not to be sufficient, the loss of some specific (?) intestinal defense machanism (bactericid substance?) is still needed for the stabilisation of pathogenic bacteria in the small intestine, resp. for the development of the inflammation. CREGAN et al. (1953) could demonstrate that the lower parts of the small intestine are generally bacterium-free even in cases of an infected stomach. It is an open question which of the two conditions is the primary one; whether enteritis develops because of anacidity or mucosal destruction is caused by repeated ascending infection from the diseased jejunum. BOGENDÖRFER (1926) thinks that enteritis is the primary pathological process in most cases.

The problem is not an easy one. Ascending infection from the jejunum is inconsistent with the common physiological sense. Under normal circumstances — in the absence of antiperistaltic waves — the intestinal contents are constantly moving downwards; the retrograde infection of upper gastrointestinal segments is quite improbable. On the other hand it is even possible that there exists no close relation between the acidity of the stomach and the enteritic changes; chronic enteritis may arise namely in the presence of various acidity levels. This assumption is supported by experiences gained during the observation of our chronic enteritis material. We could observe the appearance of chronic enteritis in patients having both low and high acidity values. We are of the opinion that chronic enteritis may be caused by a number of factors of which the effect of neural components seems to be the most important. In the presence of other promoting factors, *achlorhydry at most contributes to the development of chronic enteritis but in itself does not produce it.*

The finding of an enteritis has some practical value from the point of „anacid complaints". *Most of the digestive symptoms of achlorhydric persons are obviously of enteritic origin.* Naturally in these cases it is the enteritis and not the achlorhydry which can be treated effectively.

Summing up we may say that the disease of whichever part of the digestive system affects the function of the other digestive organs; so it can be easily understood that disorders of the liver, gallbladder and pancreas influence the gastric secretory activity. Acute inflammation increases, chronic one decreases the acid production. The mechanism is not yet understood. Reflectory effects seem the most likely but a haematogenous toxic factor may play a role too.

4. It is an interesting problem related to acid secretion whether *gastroduodenal ulcer* could ever develop withaut gastric HCl.

The well-known verdict, „no acid, no ulcer" has many adherents and opponents since it was first declared more than 40 years ago. A number of case reports has been published about ulcer (mostly gastric) patients without detectable HCl secretion. In our previous communication (VARRÓ, 1953) we emphasized that in case of an active ulcer it is not enough to demonstrate that the stomach actually does not secrete HCl, but using adequate methods it must be proved that the stomach has entirely lost its capacity to produce it.

Critically analysing the literary data with necessary restrictions as to the technique of the test meals (duration of the aspiration!) and to the choice of the stimulant used, the number of the so-called „anacid ulcers" which can be considered seriously as such is significantly reduced. PALMER (1926) made a thorough review of the subject. Until the appearance of his article the criterion of anacidity was the negative result of the Ewald test meal or some of its modification. Later PALMER and NUTTER (1940) analysed the cases reported in the literature on the basis of the negativity of a histamine test meal. Based on literary data and on their own large

material (2,200 cases) they came to the conclusion that chronic gastroduodenal ulcer does not develop but in the presence of HCl. Small acute ulcers may arise also in patients achlorhydric after the routine histamine test meal. Their opinion is shared by BOCKUS (1944) too. IVY et al. (1950) critically analysed the cases reported between 1940—1950 and came to the conclusion that no chronic ulcer occurs in persons with definite achlorhydry. As an indirect proof one may mention that no chronic ulcer or the scar of it could be demonstrated in the stomach of 800 (KAHN, 1937) respectively about 900 (WASHBURN and ROSENDAAL, 1957) deceased pernicious anaemia patients on autopsy, although it is well known that otherwise a great percentage of autopsied cases show the remnants of former gastroduodenal ulcer disease (FLEKEL, 1948). Another argument against ulcer arising in achlorhydric stomach; the development of achlorhydry either spontaneously or after irradiation leads to the healing of the existing gastric ulcer and during the period of achlorhydry no new ulcer appears (RICKETTS et al 1949a).

The following sources of error may be supposed in the diagnosis of the achlorhydric gastric ulcers published:

a) The secretory stimulant used was inadequate.

In the foregoing chapters we emphasized that the diagnosis of achlorhydry necessitates the use of histamine as secretory stimulant. Other methods cannot achieve more than rendering the existence of subacidity probable. In earlier report on anacid ulcers histamine could not yet be used and later, too, it often happens that the absence of HCl was declared on the base of a single test meal with insufficient dose of histamine.

b) Achlorhydry is diagnosed on the basis of a single gastric analysis.

Spontaneous variations of gastric acidity in the same patient using identical stimuli is a well-known fact. PALMER and NUTTER (1940) describe a case where four subsequent gastric analyses after the administration of 0,5 mg of histamine did not show the presence of HCl (the position of the duodenal tube was controlled by fluoroscopy!), but the fifth examination with the same quantity of histamine resulted in a gastric juice of 1,5 pH, having an acidity of 52 clinical degrees. IVY et al. (1950) report a patient in whom only the third histaminic test meal could reveal the presence of acid. WATKINSON and JAMES (1951) described ulcer patients who were found achlorhydric at the time of morning intubation, while gastric analysis performed later on the same day showed the presence of acid secretion.

c) The dose of histamine administered was insufficient.

In the present work we have succeeded in demonstrating that using higher histamine doses it is possible to reveal acid production even in those persons who were considered „achlorhydric" after 0,5—1,0 mg of histamine. No report is hitherto known to us which would analyse the problem of ulcer and achlorhydry using the method of the augmented histamine test, hence the possibility cannot be excluded in any „anacid ulcer" cases that the ability of the stomach to produce acid could have been detected using larger doses of histamine. For years we have been thoroughly controlling with histamine test meal all ulcer patients who were considered achlorhydric as a result of a routine gastric analysis. *Not a single case of true achlorhydry have we been able to detect in patients with ulcer disease.*

d) The existing ulcer is not the consequence of ulcer disease.

It may happen that the ulcer demonstrated in an anacid stomach is in reality an exulcerated carcinoma or the consequence of gastric tuberculosis or syphilis.

Frequently these „benign" ulcers are from the very beginning exulcerated neoplasms and only the absence of a healing tendency, metastases or other signs of malignancy call the attention to incorrect diagnosis. IVY et al. (1950) based on literary data emphasize that about 17 per cent of operated and about 6 per cent of medically treated cases of „benign gastric ulcer" turns out later to be a carcinoma.

Although gastric acid deficiency is not an obligate sign of gastric carcinoma it is undeniable that it occurs more often than either in normal persons or in ulcer patients. Even simple anacidity in an ulcer patient must give rise to the suspicion of a malignant ulcer.

Gastric tuberculosis appears most often in the form of an ulcer (KÖVES, 1948). The localisation is the same as in ulcer disease. Sometimes it is very difficult to differentiate them macroscopically, only histological examination reveals the specific nature of the lesion, which is usually accompanied by sub- or anacidity.

Although gastric ulcer of syphilitic origin is a great rarity, one must, however, think of it in a case of an anacid ulcer found in a syphilitic person. It is the consequence of an exulcerated gumma or of luetic endarteritis. Symptoms and even gastroscopic appearance are very similar to those of ulcer disease. The majority of the patients is sub- or anacid; so about 80 per cent of KÜRTHI's (1948) patients had subacid secretory patterns. One must bear in mind, however, that also syphilitic persons may have ulcer disease. It is advisable, therefore, to consider the ulcer as of syphilitic origin only if reliable proofs can be gained (good effect of Salvarsan, histological picture etc.).

To give a definite answer to the question of „anacid ulcer" is a rather delicate problem. Even in a case of true achlorhydry it cannot be excluded that at the time of ulcer development there was still some acid production. Anyhow we are of the opinion that *observations presently available do not support the idea that benign ulcer may arise and/or exist in a stomach definitevely achlorhydric*. The development of gastric ulcer and complete acid deficiency do not seem to coexist in the same stomach.

The question has some theoretical and practical implications:

From a theoretical point of view these observations support the idea that HCl plays an important role in the genesis of ulcer disease; an opinion which we do not think to be correct. In our view acid gastric juice may be only a factor of chronicity of the benign ulcer which arises as a consequence of other — mainly vascular — factors. It is not even the only factor in this field as it is known that healing of an ulcer may ensue in the presence of unchanged acidity conditions.

From a practical point of view it is important that in cases of „anacid ulcers" the achlorhydry should be repeatedly tested using adequate methods. When no HCl can be detected, the malignant, tuberculotic or syphilitic nature of the ulcer should be seriously suspected.

XI. ACHLORHYDRY AND PERNICIOUS ANAEMIA

Survey of the literary data

Soon after the first description of pernicious anaemia (ADDISON, 1855) it was noted that the disease is always accompanied by the destruction of the gastric secretory apparatus. FLINT (1860), FENWICK (1870), SCHUMANN (1875), QUINCKE (1877) and NOTHNAGEL (1879) called the attention to the remarkable atrophy of the gastric mucosa in pernicious anaemia patients.

Subsequent examinations revealed that atrophic changes are the most outspoken in the mucosa of the corpus and fundus, while the pyloric and antral part showed only mild „gastritic" alterations. The structural changes included all glandular elements, the mucosa was thin, the epithelial cells irregular. Parietal and chief cells were entirely absent or their number was greatly diminished. In the histological pictures of HENNING (1938) total atrophy of the mucosa is demonstrated. In BROWN's (1934) material parietal cells were present only in 5 specimens out of 45. MEULENGRACHT (1939), COX (1943), OLSEN and HECK (1945) and MEYERS (1948) maintain that no parietal cells can be found in the stomach of pernicious anaemia patients. Intestinal metaplasy is a frequent finding. MAGNUS and UNGLEY (1938) report that the atrophy is not only confined to the mucosa but extends to all layers of the gastric wall. On the other hand LAMBLING et al (1961) are of the opinion that the stomach of an anaemia perniciosa patient, from the biologic point of view, appears to be one that has been deprived of its parietal and chief cells but has retained normal glands of alkaline secretion.

The gastroscopic findig is by and large in accordance with the histological picture. The atrophic mucosa is of gray-yellow colour and the blood vessels in the submucosa are well visible (HENNING, 1934; UDVARDY, 1941). The gastroscopic appearence of the mucosa is, however, not always the same. Sometimes patchy atrophy (SCHINDLER, 1937), at other times entirely normal mucosa can be observed (HARDT et al. 1948). DAILEY et al. (1953) found atrophic mucosa only in about half of their 25 pernicious anaemia patients; inversely, among patients with atrophic gastritis only 13 per cent had anaemia perniciosa.

LÜHR and GÜLZOW (1938) describe gastritic changes (acute or chronic) found on gastroscopy in pernicious anaemia patients. This finding is rather exceptional, because mostly the picture of a simple atrophy is reported. Atrophic gastritis occurs not only in pernicious anaemia but in other diseases too (sprue, hypochromic anaemias, B-avitaminosis etc.).

There are divergent opinions whether effective liver therapy influences the state of the mucosa. Some authors maintain that endoscopic finding remains unchanged in haematological remission (GUTZEIT and TEITGE, 1937; UDVARDY, 1941);

HARDT et al. (1948) even describe a case where the normal mucosa became atrophic during liver therapy. Other investigators report a total (JONES et al. 1935) or partial restitution of the mucosa (LEHMANN, 1936; CHEVALLIER, 1936; SCHINDLER and SERBY, 1939). According to SCHINDLER et al. (1940 b) and SCHIFF and GOODMAN. (1940) even atrophic gastritis without pernicious anaemia can be effectively influenced by liver therapy.

Pathologists are of the opinion that the condition which on gastroscopy seems to be mucosal restitution is in reality growth of epithelial cells (COX, 1943). Lately FINCK and WOOD (1953) reexamined the problem with the aid of gastric biopsies. In spite of a complete haematological remission after B_{12} therapy, the histological picture of mucosal atrophy, the histamine refractory achlorhydria, and the apepsia remained unchanged. The same result was reported earlier after liver therapy (DOIG and WOOD, 1950).

The atrophy is thought to be the result of foregoing gastritis (FABER and BLOCH, 1900; CORNELL, 1927a; BROWN, 1934; THIELE, 1938, VELDE, 1938, etc.). According to DEBRAY et al. (1955) there is no difference but only as to the extension and irreversibility between atrophic gastritis with and without concomitant pernicious anaemia; they think that pernicious atrophy is always the result of gastritis. MAGNUS and UNGLEY (1938) do not believe in the inflammatory origin of atrophy which is in their view the consequence of hitherto unknown factors. BOCKUS (1944) thinks the atrophy to be the result of a deficiency state; he too turns against the gastritic theory. In the eclectic views of SCHINDLER and SERBY (1939), and COX (1943) inflammatory and degenerative changes coexist in the production of atrophy. The fact the pyloric region is not involved in the process would indicate a sort of selective destruction directed towards the fundic and body glands; gastritis would be only a secondary reaction. LASOVSKI (1947) states that pernicious anaemia is the result of a „total or partial loss of the regenerative capacity of the gastric glands". In WEINBERG's (1951) view there is no relation whatsoever between atrophic gastritis and pernicious anaemia; the latter is caused by the achylia gastrica (total absence of gastric secretion); mucosal changes are evoked by atrophy of disuse. HARING (1938) maintains that atrophy is the consequence of hereditary factors.

The stomach in pernicious anaemia is characterized not only by the absence of acid but also by its extreme „dryness". WILKINSON (1932) reported that the fasting stomach of pernicious anaemia patients contains an average of 15,3 ml of gastric juice whereas that of the normal stomach is 52,4 ml. Continuous gastric aspiration normally yields 150 ml/hour of gastric juice; in pernicious anaemia patients the same procedure provides 20 ml/hour, even is complete haematological remission only 46 ml/hour (GOLDHAMER, 1936, FOUTS et al. 1937). Also WINTROBE (1946) describes that he could gain but a few ml of mucous gastric juice from his pernicious anaemia patients.

Hence the main characteristic of the gastric juice in pernicious anaemia is its reduced quantity. As eventual duodenal regurgitation was not inhibited in most cases, the real quantity of pure gastric juice could be only less than reported.

As to the HCl secretion, it is generally held that the presence of acid — even in traces — renders the diagnosis of pernicious anaemia highly improbable. STURGIS (1936) could not reveal gastric acid in 600 patients studied. ASKEY (1944) reviewing all cases of pernicious anaemia with gastric acidity reported in the literature came to the conclusion that most of them do not fulfill all requirements necessary to a correct diagnosis. These are: *a)* exclusion of all possible causes which may produce

other types of macrocytic anaemias, *b)* evidence that no intrinsic factor is present in the gastric juice, *c)* effectiveness of specific (vitamine B_{12}) therapy.

It cannot be overlooked, however, that even excellent haematologists like WINTROBE reported cases with acid secretion (BEEBE and WINTROBE, 1933). IHRE (1938) maintains that some of his patients with anaemia perniciosa did secrete acid after insulin stimulation, Among 118 patients of HEILMEYER (1951) two had gastric HCl production. Cases were reported with gastric acid but with no intrinsic factor (CASTLE et al., 1931; WILKINSON, 1932; WOLF and REIMANN, 1936; MURPHY, 1948; MOVITT and LUBECK, 1953, MOLIN et al. 1955; HARRIS-JONES, 1957; and JACOBS, 1958). KINZLMEIER et al. (1952) reported that they succeeded in finding with an intragastric antimony pH-electrode in the stomach of a repeatedly controlled pernicious anaemia patient small places (in the corpus) where pH values of 1,75—1,80 were registered showing that minute areas of normal mucosa may exist which do not entirely lose the ability to produce HCl. Publications of pernicious anaemia cases with gastric acid secretion were reviewed by ALSTED (1934). In Hungary similar cases were reported by HORÁNYI (1953) and FÜREDY-SZABÓ (1955). Unfortunately many of the published data are incomplete.

In these cases an isolated lack of intrinsic factor must be supposed. In practice this is most infrequent, so achlorhydry must be considered furthermore as the most reliable diagnostical aid in pernicious anaemia.

In our view there is no causal relation between pernicious anaemia and achlorhydry. The appearence of pernicious anaemia is bound, however, to a certain degree of mucosal atrophy. During the development of atrophy, parietal cells may suffer first since they are very sensible structures with high energy demand; thus clinical achlorhydry may appear early. It is not at all surprising therefore, that several authors published cases where achlorhydry preceded by years the appearence of the anaemia. The possibility was raised (CORNELL, 1927b) that pernicious anaemia patiens did not always posses the ability to secrete HCl even before the onset of the disease. This assumption could be refuted by ROZENDAAL and WASHBURN (1938) who succeeded in collecting the results of the gastric test meals of 36 pernicious anaemia patients 2-21 years before the diagnosis was established. 34 were anacid indeed, but two of them had acidity values indicating the presence of free HCl. The same observation was reported by BÁN (1954) describing the results of gastric analyses of 17 patients performed 2-29 years before the pernicious anaemia could be discovered. He found anacidity in 14, normacidity in 1 and superacidity in 2 patients. In the two superacid cases gastric test meals were repeatedly performed and progressive development of achlorhydry could be ascertained.

Achlorhydry seems to be more frequent among the relatives of pernicious anaemia patients than in other members of the population (WILKINSON and BROCKBANK, 1931; SCHULTEN, 1934; ASKEY, 1940). The assertion of MORRISON (1938) that parietal cells produce the intrinsic factor together with HCl, seems quite improbable.

Only few investigations are known concerning the pepsin secretion of pernicious anaemia patients, but even these yield contradictory results. Some authors could not detect peptic activity (JOHANSEN, 1929; SCHEMENSKY and GELING, 1932; MALTBY, 1934); others found only traces of it (POLLAND and BLOOMFIELD, 1930; WILKINSON, 1932; HELMER et al., 1934). In single cases definite enzymatic activity could be revealed (HARTFALL, 1933; HALLÉN, 1949). It has to be mentioned that in most cases histamine was used for stimulation which is not the strongest stimulus for enzyme secretion.

The presence of bacterium coli in the gastric juice of patients suffering from pernicious anaemia is quite a regular finding. The question will be discussed in detail in the chapter dealing with the bacteriology of the achlorhydric stomach (see page 96).

In a previous chapter it has already been mentioned that BRUNSCHWIG et al. (1939) demonstrated a secretory depressant factor in the gastric juice of pernicious anaemia patients. As the same factor could be found — although with reduced activity — also in gastric juices of other people, it does not seem to be specific (BRUNSCHWIG et al. 1940).

The excretion of parenterally administered neutral red cannot generally be elicited in persons with pernicious anaemia.

A considerable progress in pernicious anaemia research was achieved after GLASS et al. (1952) reported that the intrinsic factor is identical or closely similar to that part of the gastric mucus which is produced by the mucous cells of the neck. This „glandular mucoprotein" administered together with small doses of per os B_{12} vitamin is capable of evoking haematological remission in pernicious anaemia patients. This finding is of great importance because in this way it became possible to define the intrinsic factor either as a constituent of the gastric secretion or as a substance which is adsorbed on the mucoprotein. The substance could not be isolated even by electrophoresis; various peaks could be identified with intrinsic factor-like effect (LANTNER et al. 1953). The problem needs further elucidation, but the fact seems to be established that the protecting factor of the B_{12} effect is bound to some fraction of gastric mucous substance (MACK et al. 1953; MARMION et al. 1953).

The observations mentioned clearly demonstrate that there is no causal relation between the production of intrinsic factor and gastric acid secretion. It seems an established fact that orally administered B_{12} vitamin cannot be utilized either by patients with pernicious anaemia (HEINLE et al. 1952; CALLENDER et al. 1954) or after total gastrectomy (SWENDSEID, 1953). HALSTED et al. (1954) after confirming the above data of HEINLE et al. (1952) demonstrated that the utilisation index of the orally administered B_{12} vitamin is entirely normal in non-pernicious anaemia patients with histamine refractory achlorhydry. This is a fairly good evidence that gastric HCl has nothing to do with B_{12} utilisation. Using another method SCHILLING et al. (1955) came to the same conclusions.

The problem of the interrelation between neurological changes (funicular myelosis) and gastric acid deficiency needs special attention; the question will be discussed in a separate chapter (see page 85).

Analysis of our pernicious anaemia cases

32 patients with proved pernicious anaemia could be found in our achlorhydric material. *Gastric HCl secretion could be detected in none of them,* although augmented histamine test was used in 18 patients. Similarly *neither did neutral red appear* after histamine injection in the gastric juice.

The acid instillation test after parenterally given neutral red was positive, however, in 5 out of 24 cases examined.

The bacteriological examination of the gastric juice was performed in 20 patients. Bacterium coli was found in 19 cases; in one patient pharyngeal flora appeared repeatedly. In this patient also the duodenal and jejunal juices contained pharyngeal flora.

Diarrhoea was observed in 4 patients. One of them was already analysed as to the possibility of a gastrogenous diarrhoea (see page 63), another had chronic enteritis. In two cases diarrhoea was present only in the anamnesis; actually they had normal stools. *The remaining 28 patients had no diarrhoea.*

Pathological changes of the nervous system (funicular myelosis) could be diagnosed in 13 out of 25 cases examined.

Three patients had some, chiefly painful, gastric complaints. *The other 29 persons did not mention any gastric distress.*

In 12 cases gastric peptic activity was determined; enzymatic activity was present in the gastric juices of 6 patients.

Gastroscopy was performed in 14 patients. Total atrophy was found in 9, patchy atrophy in 3 and normal mucosa in 2 patients.

Conclusions

1. The relation between achlorhydry and pernicious anaemia is not causal but only statistical. The overwhelming majority of pernicious anaemias are accompanied by achlorhydry. As the glandular elements which produce the intrinsic factor (mucous cells of the neck?) are more resistant than the parietal cells, in the period when no intrinsic factor is produced as a result of mucosal destruction, practically no parietal cell is generally present. The gastric HCl deficiency, therefore, is not a prerequisite of anaemia perniciosa; thus it is conceivable that exceptional cases of pernicious anaemia may exist with acid secretion. A few such cases are indeed published in the literature.

In spite of these rather theoretical reasonings, *clinically* achorhydry remains one of the most reliable diagnostical features of pernicious anaemia. We too failed to detect acid secretion in any of our pernicious anaemia patients.

2. The gastric mucosa of pernicious anaemia patients is characterized by atrophy. Achlorhydry (parietal cell destruction) and loss of intrinsic factor production (destruction of the mucous cells of the neck) are consequences of the atrophy. Atrophy may be of various intensity which is supported by the fact that sometimes the acid instillation test may show a positive result. The cause of atrophy is unknown; we do not think it to be of gastritic origin. The majority of pernicious anaemia patients do not have gastric complaints and it is atrophy and not gastritis that is shown by histology in most cases. In our material only 3 patients out of 32 complained of recurrent gastric distresses. The good appetite and undamaged digestion of pernicious anaemia patients were most conspicuous in the period of haematological remission.

3. The fact that pernicious anaemia patients have generally no digestive complaints proves among others that the loss of gastric digestion may be compensated by the activity of other organs of the digestive system. In about half of our cases no gastric enzyme could be detected and even in the remaining part its activity was far below the average. In spite of this — with three exceptions — no gastric symptoms were observed.

4. Gastroscopy does not always furnish reliable evidence as to mucosal atrophy because in mild cases the investigator may qualify the finding as normal. The cause of this error lies probably in the compensatory growth of epithelial cells. It is sometimes also very difficult for the gastroscopist to differentiate between atrophy and atrophic gastritis. Sometimes only histology can establish the correct diagnosis.

5. Pernicious anaemia is a deficiency disease, caused by the deficiency of the intrinsic factor. As this latter is the product of the gastric mucosa, total mucosal atrophy always evokes pernicious anaemia.

XII. VARIOUS DISEASES WHICH MAY BE ACCOMPANIED BY ACHLORHYDRY

A number of pathological processes besides causing specific changes may result in decreasing or stopping the gastric acid secretion. Sometimes the disease is confined to the stomach (e. g. carcinoma), on another occasion remote organs (e. g. thyreoidea) or the whole body (e. g. tuberculosis) are involved. We do not want to discuss all possibilities which may produce gastric secretory depression, but to mention briefly the relation of some important diseases to achlorhydry.

We must emphasize that in the majority of the cases mentioned below the achlorhydry is not a true one; mostly only a significant decrease of HCl secretion can be observed.

The possibilities may be classified as follows:

1. *Secretory stimuli weaken or inhibitory stimuli become more intensive:*
a) neurovegetative dystony, psychoses, depressive conditions, emotional factors
b) diabetes mellitus
c) hyperthyreosis
d) gravidity
e) cholecystitis, enteritis

2. *The metabolism of the secretory glands is disturbed:*
a) fever
b) anaemias (with significantly lowered erythrocyte count)
c) congestive heart failure
d) hepathopathies
e) deficiency diseases
f) chronic renal insufficiency
g) endocrine disturbances

3. *Anatomical changes of the secretory system:*
a) degenerative changes
senile involution
pernicious anaemia and other atrophies
b) chronic inflammation
gastritis
chronic infection (tbc. syphilis)
c) mucosal destruction (malignancies)

Ad 1./*a* These possibilities will be discussed in the chapter dealing with the servous system (see page 85).

Ad 1./*b* Lower than normal secretory values have been reported in diabetes mellitus. DOTEVALL (1961) reported that achlorhydria is common in diabetics. 17 per cent of

his diabetes patients examined with maximal histamine stimulation had no gastric HCl. Chronic atrophic gastritis was histologically demonstrated in all cases with achlorhydria and was associated with blood vessel lesions in the tunica mucosae. The author's opinion is that nutritional disturbances in the gastric mucosa caused by the vessel lesions may be a contributing factor in the development of chronic atrophic gastritis in diabetics.

But there are contrary views as well. So MOHNIKE (1955) frequently met normacidity and even superacidity in his large diabetic material. Low acidity values would be the result of the secretion-decreasing effect of high blood sugar level.

FENZ (1938) reported that about half of his diabetes patients were anacid after a coffeine test meal; the rate of anacidity being even higher in untreated cases. 44 out of 116 patients suffered from diarrhoea which he considered to be gastrogenous. *In our view the majority of diabetic diarrhoeas are caused by concomitant enteritis, whilst sometimes they are consequences of neurovegetative disturbances (nocturnal diarrhoea).*

ad 1./*c* Anacidity is frequently met with in hyperthyroidism but sometimes it may be observed also in myxoedema. VEDDER (1930) found anacidity in the majority of his patients with Graves' disease. Essentially the same finding was reported by MOLL and SCOTT (1927), LOCKWOOD (1925), LERMANN and MEANS (1932) and KLEINER and RÉNYI-VÁMOS (1937). R. SCHMIDT (1932 a) described that after thyroidectomy acidity began to rise; he speaks therefore of a „thyrotoxic inhibition". WILKINSON (1933) performed gastric analysis in 100 patiens with hyperthyroidism; the rate of achlorhydry was 36 per cent. The same rate in 114 patients after thyroidectomy was only about 10 per cent. He controlled 25 thyrotoxic patients who were achlorhydric before the operation; only 3 of them had no acid secretion after successful thyroidectomy. Among the 36 achlorhydric, thyrotoxic patients 30 had basal metabolic rate above + 35% and only 6 below this value. In spite of this he is of the opinion that as to anacidity it is not the value of the basal metabolic rate but the existence of thyroid hyperfunction which is of decisive importance.

The acid secretion which appears after thyroidectomy renders highly probable that the secretory depression frequently found in thyrotoxic patients is caused by functional inhibition.

Hypercalcaemia may significantly lower gastric acid secretion (BABKIN et al. 1940).

ad 1./*e* See the chapter dealing with digestive diseases (page 73).

ad 2./*a* The secretion-decreasing effect of fever has been demonstrated in several observations; for a review of the literary data see the work of BANDES et al. (1948). The exact mechanism is not yet wholly understood, Pyrogens decrease gastric secretion even if the development of fever is inhibited by drugs (OLSON et al. 1954).

ad 2./*c* Cardiac patients in compensated state are rather superacid, but in decompensation they become anacid. In our view the secretory depression observed is the result of hypoxy caused by chronic circulatory failure.

ad 2./*e* Deficiency states (pellagra, beri-beri, sprue, chronic malnutrition), especially advanced cases, are generally followed by anacidity. It may be presumed that acid deficiency is caused by metabolic changes in the glandular elements of the stomach. In this respect vitamins seem to have minor importance. A-avitaminosis, e. g., does not influence the secretory response after histamine in dogs (HERRIN, 1940). Guinea pigs with C-vitamin deficiency have also a normal posthistaminic acid secretion (NORDSTRÖM, 1939).

The food ingested exerts a certain influence on the development of the individual secretory type. So CLOETTA (1902) raised two puppies on a diet containing milk and iron, other two got meat. The former became achlorhydric, the latter superacid. Microscopically the gastric mucosa was normal in the achlorhydric animals.

ad 2./*f* Gastric mucosa of about 50 per cent of uraemic patients show the picture of chronic gastritis. The reason may be the compensatory excretion of nitrogenous substances. The gastric juice of uraemic patients is generally anacid while that of other renal patients with normal nonprotein nitrogen is rather superacid (W. HENNING, 1938).

ad 2./*g* The majority of 38 patients with chronic adrenal insufficiency examined by ROWNTREE and SNALL (1931) were sub- or anacid. The same finding was reported by FEYRTER and KLIMA (1952). No acid secretion could be evoked by giving 0,5 mg of histamine in the Addison-patients of STEMPIEN and DAGRADI (1954). During steroid therapy (DCA, Cortisone) the acid secretion reappeared. Macroscopically the mucosa seemed to be normal in both periods. TUERKISCHER and WERTHEIMER (1945) reported that both quantity and acid and enzyme content of gastric secretion is significantly reduced in adrenalectomised rats. Isolated ablation of adrenal medulla did not produce this effect. Normal secretory conditions could be restored by giving total adrenal extract but not with DCA or NaCl.

85 per cent of patients with hypophyseal cachexia had sub- or anacidity (ESCAMILLA and LISSER, 1942). KYLE (1955) published a case of Simmonds' disease with histamine refractory achlorhydry and endoscopic atrophy. After a cortisone treatment of 8 months duration he succeeded in getting a gastric juice of 40 clinical degrees of acidity with a simple test meal and the gastroscopic picture of the mucosa too became normal. The gastrointestinal mucosa becomes atrophic after hypophysectomy and adrenalectomy in cats (HAEGER et al. 1953).

There is an interesting and not clarified relation between chronic arthritis and acid deficiency; it is remarkable that these anacidities are mostly symptomless. MILLER and SMITH (1927) on the basis of 250 observations maintain that anacidity is five times more frequent in chronic arthritis than in healthy persons. 20 per cent of EDSTRÖM's (1939) 432 rheumatoid arthritis patients were histamine refractory achlorhydrics, another 10 per cent had very low acidity values. After amelioration part of them began to secrete HCl.

XIII. ACHLORHYDRY AND THE NERVOUS SYSTEM

A) *Relation between myelopathy and achlorhydry*

The interrelation between funicular myelosis (myelopathy) and pernicious anaemia has been well known since the first publication of LICHTHEIM (1887). Before the introduction of liver therapy, in the time of grave and progressive anaemias (hence the term „pernicious"!) it was generally held that neurological symptoms are caused by the anaemia. But it was soon observed that there is no strict parallelism between the gravity of the anaemia and the spinal symptoms; sometimes, neurological symptoms appeared and/or were fatal before severe anaemia developed. As soon as it became evident that pernicious anaemia is caused by the deficiency of a gastric „intrinsic factor", it was suspected that pathological changes of the stomach may be responsible for the development of neural symptoms as well.

Various explanations may exist for the interrelation between gastric mucosal function and neural symptoms:

a) *Deficiency of gastric HCl*

This idea is supported by the observation that achlorhydry is a general finding, not only in pernicious anaemia but also in other diseases which are accompanied by funicular myelosis. So both achlorhydry and funicular myelosis have been described to occur in leukaemia, sprue, diabetes, hyperthyroidism, nephritis, beri-beri, pellagra etc. GERÉB (1948) thoroughly reviewing the literary data states that achlorhydry can be either supposed or is demonstrated in all non-pernicious anaemia patients with funicular myelosis. LAFON et al. (1954) consider the acid deficiency to be the primary factor of the development of myelopathy. As a counter-argument one may mention that sometimes funicular myelosis could be observed in normacid patients (ZEMAN and DELAND 1957), and several achlorhydric or even pernicious anaemia patients can be found without the slightest sign of funicular myelosis. In our material too we have encountered true achlorhydric persons without any pathological neurogenic sign or symptom. In the chapter dealing with pernicious anaemia we have emphasized that the acid deficiency in itself is not the causative factor of the anaemia, but has only diagnostical importance as a reliable indicator of mucosal damage. We shall try to demonstrate further (see page 90) that using the augmented histamine test it is possible to detect acid secretion even in some of those funicular myelosis patients who were considered „histamine refractory anacid" after a routine gastric analysis.

b) *Deficiency of the antipernicious factor*

Effective liver therapy or vitamin B_{12} administration not only produces haematological remission but may stop the progression or sometimes — especially in mild cases — even cause amelioration of the neural symptoms. Funicular myelosis is considered, therefore, by some authors as a special consequence of vitamine B_{12} deficiency; the appearence and nature of the pathological manifestations depend only on the actual reactivity of the haemopoetic- or nervous system. That is why UNGLEY (1949) declares that the supposition of the existence of a special factor affecting the nervous system, the so called „neuropoietin" is unwarranted. Through changes in cellular metabolism the deficiency of vitamin B_{12} may produce both the haematological and nervous disorders. This assumption is supported by the fact that sometimes a thorough haematological examination performed after the appearance of funicular myelosis may detect discrete signs of pernicious anaemia: a moderate decrease of the erythrocyte count, the beginning megaloblastic transformation of the bone marrow and an increase in the volume and diameter of the red blood cells. JEWESBURRY (1954) reported 5 cases of combined degeneration of the cord with normal haematological finding both in the periphery and in the bone marrow; later, however, pernicious anaemia developed in two of them. Similar cases were reported by BOUDIN et al. (1954) as well. Inversely, thorough neurological checkings on pernicious anaemia patients lead to the discovery of several mild cases of funicular myelosis.

It is undeniable that the majority of funicular myelosis patients come from the pernicious anaemia group. Symptoms of myelopathy were observed without haematological alterations in some patients after subtotal gastrectomy; the introduction of a vitamine B_{12} therapy resulted in complete recovery also in this group (BASTRUP—MADSEN, 1954).

The absorption of labelled B_{12} was defective in patients having funicular myelosis but no anaemia which would prove the deficiency of the intrinsic factor (ARIAS et al. 1955). The examination of B_{12} absorption seems to be important also in myelopathies without haematological alterations.

Certain circumstances should be emphasized which render the definite solution of the problem most difficult. Thus the discovery of discrete neurological or haematological signs depends on the skill of the investigator. In the view of a neurologist e. g. the frequency of neurologic complications in pernicious anaemia would reach 70—80 per cent, haematologists, however, do not consider it to be more than 8—10 per cent (BODECHTEL, 1953). This is also true inversely; neurologists do not frequently perform detailed haematological investigations and thus some haematological changes which occur in funicular myelosis remain undiscovered. Another difficulty is the criterion of the correct diagnosis of funicular myelosis. There is no full agreement as to minimal signs or symptoms which would already prove the existence of combined degeneration (ORBÁN 1954). Some authors are of the opinion that „mutatis mutandis" the observation of a simple paraesthesia already warrants the diagnosis of funicular myelosis, others think that the loss of the vibration sense and the impairment of the position sense must be considered as minimal requirements for the diagnosis. Some even maintain that only in the presence of objective and definite neurologic signs can funicular myelosis be diagnosed. The rate of occurrence naturally changes according to the standpoint of the author in this question. GERÉB (1948) stoutly maintains that neurologic signs alone are not sufficient for the diagnosis.

BODECHTEL (1953) states that the correct analysis of the histological picture needs a well-trained investigator.

As an argument against the decisive role of the antipernicious factor in the development of funicular myelosis may be mentioned that there are cases where even thorough haematological investigation cannot detect pernicious anaemia, but funicular myelosis is undoubtedly present. About 30 per cent of BODECHTEL's (1953) patients did not have pernicious anaemia. Sometimes a concomitant disease may be found which is aetiologically related to the neural symptoms. LEHOCZKY (1950) reported 36—40 various disorders which are sometimes accompanied by funicular myelosis. SALUS and REIMANN (1934) claimed to have furnished an important evidence against the exclusive role of the intrinsic factor: they described having detected some intrinsic factor in the gastric juice of a funicular myelosis patient.

c) *The bact. coli population of the gastrointestinal tract*

A certain importance is ascribed in the development of neurogenic symptoms to the nearly permanent bact. coli colonisation of the upper gastrointestinal tract. This theory was in the focus of interest until the discovery of the antipernicious factor. SALUS (1932) e. g. demonstrated coli antibodies in the cerebrospinal fluid of three non-pernicious funicular myelosis patients and declared that the bacteria must play a role in the aetiology. The presence of bact. coli in the gastric juice in pernicious anaemia is almost a regular finding. It does not seem, however, to be bound to haematologic changes but to mucosal destruction as one may often find it in non-pernicious patients with true achlorhydry. We have observed funicular myelosis without the presence of bact. coli as well.

d) *Extensive functional impairment of the gastric mucosa*

This is, in our view, the link between achlorhydry, pernicious anaemia and funicular myelosis. Mucosal damage results first in acid deficiency. If the destructive process is progressive, achlorhydry already points to forthcoming intrinsic factor deficiency resp. anaemia. The mucosal lesion is in relation with the neurogenic symptoms too. Funicular myelosis may be observed, therefore, in cases without the haematologic picture of pernicious anaemia but with a seriously impaired gastric mucosa caused by cellular metabolic defect (beri-beri, pellagra) toxic inhibition (leukaemia, tbc, nephritis) or other systemic reason.

The question cannot be answered yet why once the haematologic another time the neurogenic disorder stands in the foreground. It is possible that two distinct but related substances are secreted by the stomach but neither can it be excluded that the various reactivity of the two organ systems may define the localisation of the pathological process.

This our concept, which contributes to the functional impairment of the gastric mucosa a decisive role in the pathogenesis of funicular myelosis, does away with the difficulty of interpreting the genesis of funicular myelosis cases with and without pernicious anaemia. *Thus not only irreversible mucosal damage or deficiency of the intrinsic factor may evoke the neurogenic symptoms but the long-lasting inhibition of gastric mucosal function as well.* FEUDELL (1954) reported a case of funicular myelosis caused by gastric carcinoma; the patient was histamine refractory achlorhydric. None of JEWERSBURY's (1954) seven non-anaemic funicular myelosis patients

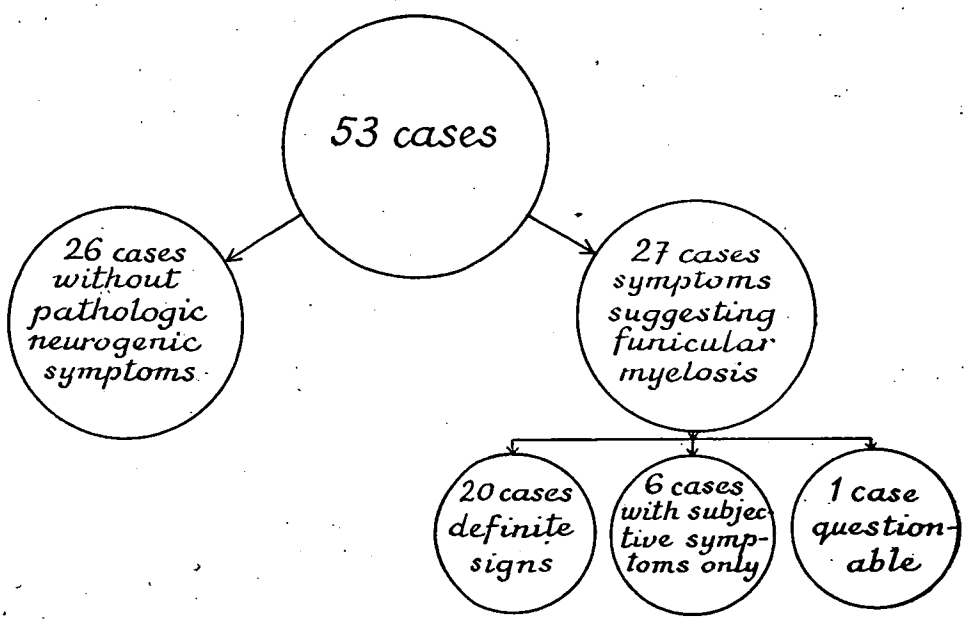
secreted acid after histamine. BASTRUP-MADSEN's (1954) patients after subtotal gastrectomy who developed myelopathy were achlorhydric too. COMINSKY and HOLAVKO (1954) described untreated cases of anaemia and funicular myelosis with normal blood marrow finding; gastric analysis did not show acid secretion. The few examples cited demonstrate that gastric secretory failure may be found in most cases of non-pernicious funicular myelosis. Unfortunately one may often find case reports where the result of the test meal is not mentioned.

The neurogenic symptoms are caused not only by a certain functional impairment of the gastric mucosa but also when the absorption of the gastric factor produced is disturbed. This is documented by case reports on ileocolic fistula patients developing signs of funicular myelosis (e. g. WILKINSON 1955). The importance of a possible malabsorption is stressed by HUSZÁK and GERÉB (1947) who demonstrated low vitamin-A levels in their funicular myelosis patients. The pertinent literature on malabsorption of vitamine B_{12} in funicular myelosis has been summarized by RICHMOND and DAVIDSON (1958).

That is why ROBERTSON et al. (1955) recommend in all suspected cases of myelopathy to perform gastric biopsy and to begin preventive vitamin B_{12} therapy if the histology of the excised mucosal piece shows signs of atrophy. In their published case the haematologic picture was entirely normal at the time of the bioptic

Figure 10.

Neurogenic symptoms in achlorhydrics.



diagnosis of gastric mucosal atrophy; neurogenic symptoms were mild and inconclusive. After the elapse of five years without any treatment the patient returned showing the complete haematological and neurological picture of anaemia perniciosa.

Our own investigations

The data of our neurological investigations are shown in Figure 10.

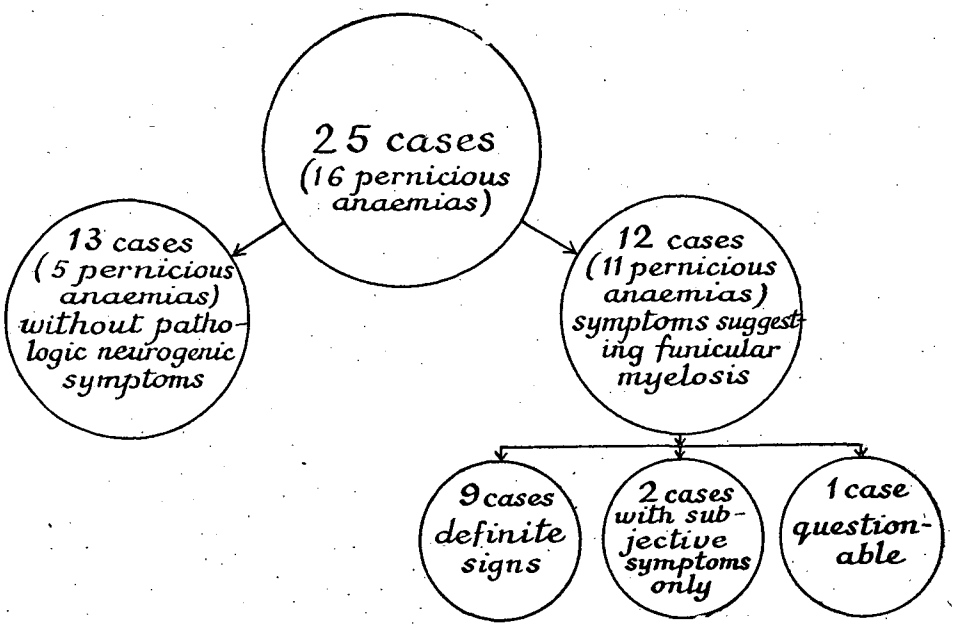
In 20 out of 53 achlorhydric patients examined we were able to demonstrate definite signs of funicular myelosis, in 6 cases a tentative diagnosis was made and one patient was suspected to have myelopathy. In 26 no pathologic neurogenic signs were detected.

The diagnosis of funicular myelosis was based on the following criteria: impaired deep sensibility: lost or diminished vibration sense, ataxia, areflexia or unequal reflexes were considered as *definite* signs; the subjective symptoms of a poorly defined hyp-or hyperaesthesia and paraesthesia were taken as doubtful signs.

After analysing the 25 patients without acid secretion even after 3 mg of histamine we found 9 cases of sure funicular myelosis; the diagnosis was tentative in two patients and suspected in one. 11 out of the 12 funicular myelosis patients came from the pernicious anaemia group. Altogether we performed neurologic examinations in 16 pernicious anaemia patients and 11 of them had signs related to funicular myelosis. (Figure 11.)

Figure 11.

Neurogenic symptoms in true achlorhydrics.

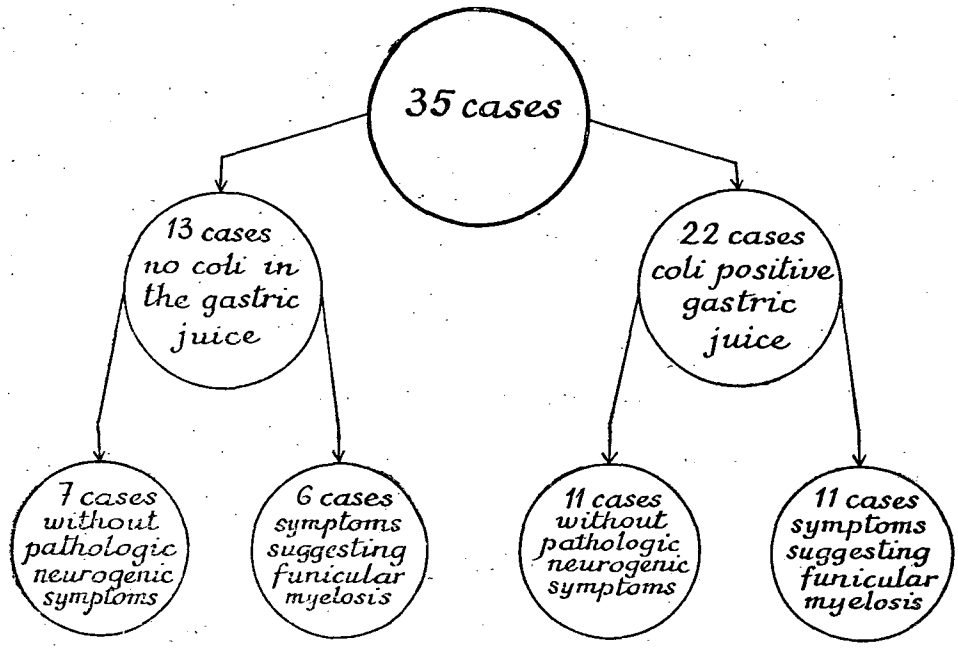


In the group showing definite signs of myelopathy 4 patients secreted HCl during the augmented histamine test. This clearly shows that the presence of gastric acid does not exclude the diagnosis of funicular myelosis.

In 22 cases out of 35 examined could bact. coli be detected in the gastric juice. Of the coli positive cases 11 showed signs of funicular myelosis, but the other 11 had no neurogenic symptoms. In six patients with definite signs of myelopathy no bact. coli could be demonstrated in the gastric juice; this our finding is a conclusive evidence against the bact. coli being the causative agent. (Figure 12.)

Figure 12.

The interrelation between the coli positivity of the gastric juice and the neurogenic symptoms.



Conclusions

1. The analysis of our achlorhydric material demonstrates that about the half of the patients examined had neurologic signs related to funicular myelosis. Neurogenic symptoms generally are discrete and cause little trouble It is interesting that only in a part of our myelopathy patients could perniciouslike anaemia be detected (in 11 out of 27); from a haematological point of view the other patients had to be considered normal.

2. *The appearence of the neurogenic symptoms is not necessarily bound to total acid deficiency.* The diagnosis of funicular myelosis could be established in persons

who were found to secrete HCl during the augmented histamine test. Neither can the gastric coli infection be considered as an obligatory prerequisite for the development of funicular myelosis, as typical neurogenic symptoms were observed with no coli in the gastric juice. So the definite standpoint can be assumed that *neither achlorhydry nor gastric coli infection are absolutely necessary for the development of funicular myelosis.* It is undeniable that in the majority of cases funicular myelosis occurs in patients having an achlorhydric stomach infected with bact. coli; both conditions are, however, only indicators of mucosal destruction. That is why we are of the opinion that serious functional impairment of the gastric mucosa is an important (although not exclusive) factor in the genesis of funicular myelosis.

3. As the greater part of our funicular myelosis patients were not anaemic at the time of the neurologic examination, it seems to be of importance that all achlorhydric subjects — irrespective of their haematological status — should undergo a thorough neurologic examination. If the suspicion of funicular myelosis arises, it is advisable to begin with the B_{12} therapy — irrespective of the eventually normal haematologic status — in order to prevent later appearing irreversible neurologic changes.

B) *The relationship between psychic reactivity and gastric acid deficiency*

Among the factors which may possess certain importance in the development of achlorhydry the effect of higher nervous activity and emotional reactions on gastric mucosal function should be mentioned. As discussed before, in the majority of anacid persons inflammation, toxic influence, reflex inhibition, metabolic defect or degenerative changes contribute to the loss of acid secretory capacity. There are cases, however, where none of the above factors can be detected either in the anamnesis or during actual examination, but there is ample evidence to suspect a close relation between secretory depression and the psychic reactivity. At present this interrelation is still far from being cleared up. Even the fundamental question is not yet decided whether a certain psychic reactivity causes the secretory anomaly or inversely morbid conditions with abnormal secretory pattern result in some sort of psychical disorder.

The effect of emotional factors on gastric secretion is a long established fact. In experimental animals all emotional upset leads to secretory inhibition. So BICKEL and SASAKI (1905) demonstrated that in dogs the secretory reaction to sham-feeding was markedly diminished when a cat was brought into the room.

The inhibitory effect of an emotional distress on gastric secretion was observed in man too. BEAUMONT (1833) mentions fear and anger as inhibitory factors. HEYER (1922) could evoke the lowering of gastric secretion with hypnosis. WITTKOWER (1931) suggested different kinds of emotions during hypnosis and observed an individual variation of the secretory reaction after the same sort of suggestion. He allegedly produced a histamine refractory achlorhydry merely by hypnosis. HEILIG and HOFF (1925) produced transitory acid deficiency by suggesting the eating of disgusting food. The communication of BECKER (1934) merits special interest; he repeatedly found anacidity in a convict during his imprisonment; after he was discharged the acid secretion began to normalize. BUMKE (1936) in his handbook makes mention of the experience that depressive conditions can evoke even histamine refractory achlorhydry.

One has to remember, however, that secretory patterns show a considerable variation even in the same individual which sometimes casts doubt on the actual existence of an interrelation between the increase or decrease of acid secretion and the emotional change. In this respect the interesting observation of HOELZEL (1942) should be seriously considered. He controlled his own acidity values daily for years and found them to vary between (0,0-0,13% of HCl on fasting stomach. As a result of a great excitement and the fear and anxiety which followed it, he experienced a prolonged increase in acidity which returned to normal only after he became definitively calmed down.

So the influence of emotional factors on the secretory activity of the gastric glands seems to be established. It remains an open question whether the psychic depressive factors — probably through atrophy of disuse — may result in a definitive achlorhydry. Based on literary data and on our own clinical experience, this possibility cannot be excluded.

Psychological investigations were carried out on some of our achlorhydric patients to elucidate the possible relation between the psychic reactivity and the secretory anomaly.

Methods

At first the widely used Rohrschach test was employed. As the psychic examinations were not performed on in-patients of the Dept. of Neurology in the course of a long observation, but during one or two ambulatory conversations, this method was considered the most suitable, naturally besides thoroughly working up the anamnestic data and performing psychic exploration. The same test was usually employed also in ulcer disease, so to make a comparison with the ulcer patients this method seemed most useful. Besides all patients were tested with a questionnaire composed by ourselves. The questions were composed in a manner which made it certain that the individual reactivity to psychomotoric and psychosensoric stimulation and the equilibrium of the vegetative activity would be equally tested. The questions were completed with such as reflected the general reactivity of the nervous system, the patient's relation to other people and the outside world.

Examples for the establishment of motoric rectivity:

Working ability?

Does trembling appear while working or during other burden? Judging the mimic.

Examples for the establishment of psychosensoric rectivity:

Hypersensibility against any stimuli?

In which organs do the emotions generally cause complaints?

Examples for the establishment of vegetative nervous activity:

Appetite, fluid intake, troubles of the sexual sphere, sweating, disposition to turn red or pale, pupillary reactions, dermographism.

Examples for the establishment of higher nervous activity:

Interest, learning, forgetfulness, will-power, self-confidence, attitude to the family and the surroundings. Emotional reactions.

In some cases the so called neurotic questionnaire-test of EYSENCK (1953) was employed as well. As to the literature of the test methods we refer to the book of

STERN (1954). For the evaluation of the Rohrschach test the handbook of BOHM (1951) was of great help. As to the questionnaire-test the articles of BODA (1942) and ÁNGYÁN and KAJTOR (1956) served as helpful guides.

Results

Psychological examinations were performed in 34 achlorhydric persons.

With the Rohrschach test it was surprising that a great number of achlorhydric subjects furnished a high percentage of such anatomical responses as had to be considered abnormal. Besides, Md and Td answers occured in a great number, B answers were lacking. Relatively often Dzw answers could be found as well. In another part of the patients colour naming, symmetry answers, perseveration and light-dark answers occurred in a considerable number.

From the results of the questionnaire-test one may conclude that in the overwhelming majority of the patients the vigour of the nervous processes seemed to be weakened. One may especially emphasize the hyperirritability against various stimuli, the imbalance of the nervous processes and the lability of the vegetative sphere. As to the latter the activity of the gastrointestinal system was particularly followed with attention. In a great part of our patients the diminished agility of the nervous processes, a certain passivity towards the surrounding but good capability of adaptation could be observed.

It should be noticed that according to the intention of the investigations only substantial and conspicuous signs of the Rohrschach test were evaluated; a profound analysis of the personality was not attempted.

We succeeded in differentiating three groups:

a) Anxious, depressive patients, full of fear; 17 persons were placed in this group.

b) Patients showing autistic, eccentric (schizoid), psychopathic symptoms; 9 patients were placed in this group.

c) Patients showing normal psychic traits; 8 persons were placed in this group.

In 25 patients it was examined whether in the case of excitement, emotion, botheration they had somatic complaints localised to the gastrointestinal tract or rather, which of their organs had been hypersensible since their childhood. 15 out 25 persons reported that the hyperirritability and the malfunctioning of the gastrointestinal tract ran right through their lives. In this respect no difference could be detected in the above groups.

It was equally analysed how many patients are found in the various groups with no gastric and/or intestinal complaints in the anamnesis or at the time of the neurologic investigation. 17 out of the 34 persons examined had no such complaints, 11 patients had gastric and 6 other intestinal symptoms.

The occurrence of the gastrointestinal symptoms in the various groups is demonstrated in Table 12.

Discussion

In the course of the psychologic analysis of our achlorhydric material we could ascertain that disturbances of the emotional sphere can often be observed. The frequency of psychopathologic traits in the achlorhydric group studied is undoubtedly greater than in other mentally normal population.

Table 12.

The interrelation between the presence of gastrointestinal symptoms and the types of psychic reaction

Types of psychic reaction	Case number	Gastrointestinal complaints		Symptomless
		gastric symptoms	intestinal symptoms only	
Patients showing normal psychic traits	8	2	1	5
Patients inclined to autism	9	5	1	3
Depressive patients	17	4	4	9
Total number	34	11	6	17

To decide whether the psychic findings are specific for the secretory anomaly, we tried to compare our data with those which were gained during the analysis of duodenal ulcer patients, this disease being accompanied mostly by superacidity. Unfortunately it is not easy to find investigations where the psychologic analysis of gastric and duodenal patients were performed separately, although it is known that the two types of ulcer are quite distinct as to the nature of gastric secretory reaction. We cannot speak about the predominance of superacidity but in the cases of duodenal ulcer, the majority of gastric ulcer patients being rather subacid.

From this point of view the monography of WRETMARK (1953) is of particular interest. He maintains that gastric ulcer patients do not seem to differ from others in any remarkable way. On the other hand duodenal ulcer individuals are generally supercapable (intelligence above average) and of unbalanced (non-syntonic), cool, unfriendly personality; behind the latter traits one may find, however, a timid, cautious and non self-reliant psychic mind. DRAPER and MCGRAW (1927) are of the opinion that chronic anxiety, the feeling of incertitude and psychic inferiority are decisive factors in the psychodynamics of the ulcer disease. ALEXANDER (1934) is rather sceptical about the existence of a specific psychic factor which would cause gastric symptoms. As a psychoanalyst he considers most important whether the conscious emotions and their tendencies may be expressed freely and whether an alleviation occurs. He considers the actual life-situation only as a trigger mechanism. MITTELMANN and WOLFF (1942) think that anxiety, incertitude, anger, guilty conscience, frustration of desires and plans are of primary importance. They state that disagreable, dysphoric affections increase the gastric acid secretion.

Some of the authors try to describe a specific „ulcer-type", others deny the possibility of the existence of a definite „ulcer-personality". In our view *the psychic factors mentioned do not show any specificity,* one cannot state more than that *emotional disturbances probably have some influence on the development of gastroduodenal ulcer.* Chronic fear, anxiety, incertitude, these are the emotional factors which can be often observed in ulcer (mostly duodenal) patients. We must not forget that these same emotional factors could be observed in a considerable portion of our achlorhydric patients as well. This clearly shows that from the point of

view of superacidity it is not the nature of the emotions or the specificity of some psychic factors which is of utmost importance but rather the gastric secretory reactivity of a given individual. Thus superacidity (and e. g. duodenal ulcer) may ensue in an individual with certain psychic reactions on certain emotional factors, while the same factors produce subsecretory response in other persons. Consequently there is no „superacid (ulcerous)-personality" or „anacid personality" but the actual individual reactivity decides what sort of secretory response ensues as the result of certain emotional disturbances.

It is possible that superacidity is followed by subacidity in the same individual as a consequence of the same psychic influence in various periods of his life according to the actual reactivity of the stomach. Such mechanism may intervene in the life of a gastritic person where superacid periods are followed by subacid and finally by anacid ones. Although here recurrent infections seem to play the decisive role, in our view neither can the effect of neurogenic factors be neglected.

The possibility has already been mentioned that — similarly to ulcer disease — the secretory disorder would not be the result of emotional, psychic disturbances but inversely, the secretory anomaly and the diseases which follow it, would result in psychic changes. This theory has but few adherents even in the field of the ulcer disease. Related to our achlorhydric material it seems even less probable, as in about half of the patients no digestive symptoms could have been detected. Thus the gastrointestinal complaints as starting point for the psychic alterations cannot seriously be taken into consideration.

As a fact, depression and anxiety can be met most frequently but we have no data how often they are accompanied by super- or anacidity. This our work cannot support evidence in this respect as it treats the problem not from the point of view of the depressive emotional disturbance but from that of the achlorhydry. All we can say is that psychologic examination in achlorhydrics often reveals fear, anxiety and depression.

Reviewing our findings we may say that *we found in a great percentage of our achlorhydric patients tendency to anxiety, depressive traits and vegetative lability with pronounced gastrointestinal predominancy.* As similar traits were encountered — according to literary data — also in gastroduodenal ulcer patients, we must conclude that these psychic reactions are by no means specific to gastric acid deficiency. Emotional disturbances undoubtedly exert some influence, but the secretory reaction depends entirely on the reactivity of the gastric glands.

XIV. THE BACTERIOLOGY OF THE ACHLORHYDRIC STOMACH

Survey of literature

The normal gastric juice is sterile or contains only scarce pharyngeal flora, the latter reaching the stomach through swallowing. It is generally held that the sterility of the gastric contents is the consequence of the HCl production. The strong acidic surrounding is unsuited to the growth of the microbes. Because of the loss of the „acid barriere" one may find in the stomach and in the upper part of the small intestine of achlorhydric persons a mixed flora containing mostly members of the coli group.

VAN DER REIS (1921) stated that the bactericidal effect of the gastric juice is not the same on various sorts of bacteria. The effect of an aqueous HCl solution seemed to be weaker than that of a gastric juice of corresponding acidity. ARNOLD's (1927) experiments showed that the gastric acidity has a decisive importance in the maintenance of the acidic milieu in the duodenum and the jejunum. A shift in alkaline direction results in the establishment of an external bacterial flora. JARNO and SURÁNYI (1929) attach importance in the development of bactericidal effect to the bile acids which are mixed in a certain concentration to the gastric juice. In their view cholic acid which is split from bile acids in the presence of free HCl would be the factor which enhances the bactericidal capacity of the gastric juice. HENNING (1930) observed no bacteria in about half of the normal gastric juices examined; in the rest he found a few colonies of Gram-positive streptococci (streptococcus lacticus) and bacilli (bact. lacticum), some staphylococci, fungi, sarcinae and enterococci. The same finding could be observed in chronic gastritis cases with norm- or superacidity. In subacid gastritis the haemolytic streptococcus was the dominant type; he could not find coli but in one case. Anacid persons had an abundant flora. Especially high percentage of coli positivity was encountered in histamine refractory achlorhydric subjects. In coli positive cases he always diagnosed atrophic gastritis endoscopically, for this reason he thinks that in cases of coli positivity a gastric atrophy is always simultaneously present. As most cases of pseudo-achylias yield a normal flora, he recommends for the differentiation of the achylias the bacteriological examination of the fasting gastric contents. He considers that the bacteria found in normal stomachs are only temporary guests; they are introduced with the food and destroyed by the acid gastric juice. The decisive factor is the HCl, gastric juice would contain no other bactericidal substance. Bact. coli strains are especially sensitive to HCl, they are destroyed even by a subacid gastric juice. The bacteria are leaving the anacid stomach too, but reach the small intestine alive. KLINGE (1930) found a sterile gastric juice in 11 out of 12 cases of „functional anacidity" (he did not find the cause!); in „organic anacidities" various bacteria were observed. Especially

abundant coli flora was encountered in pernicious anaemia and gastric carcinoma He considers that anacidity itself is not sufficient for the growth of coli, also gastritis is needed. BRINCK (1933 a) examining 400 acid gastric juices (using caffeine or histamine) found microbes belonging to the coli-aerogenes group in 25 instances. The positive bacterial finding can be explained in his view by an ascending infection from the intestine (enteritis) or from the gall bladder (cholecystitis). Sometimes the finding was only an occasional one: in repeated examinations no bacteria were detected. In a patient after intensive atropine dosage a temporary anacidity could be encountered, simultaneously coli made its appearence in the gastric juice. He thought that not only the gastric secretory inhibition but also the decrease of the intestinal secretion contributed to the upward migration of the bacteria, first into the small intestine and from here into the stomach. Thus the direction of the process is not gastritis (anacidity) and then enteritis, but inversely, first the flora of the small intestine changes and the bacteria cause gastritis afterwards through ascension.

BRINCK and WICHELS (1933) could reveal sterile gastric juice only in 6 out of 104 anacid patients (pernicious anaemia, gastric carcinoma and postgastrectomy cases excluded). They found partly Gram-positive (mostly pharyngeal but occasionally intestinal flora), partly Gram- negative (coli-aerogenes group) organisms. They believe that in the stomach Gram-negative bacteria indicate always organic mucosal lesion. They did not find a noteworthy parallelism between the gastric symptoms and the bacteriological finding of the stomach.

Besides gastric HCl, BRINCK (1933 b) contributes a minor role in the bactericidal action also to the thiocyanates present. In anacid persons the thiocyanate level of the gastric juice is generally low, but in those persons who had a sterile gastric juice in spite of their anacidity the same was found elevated. The correlation is only statistical, there are several exceptions. BRINCK himself is of the opinion that the thiocyanate only potentiates the bactericidal effect of the HCl, more precisely, of the H ions. Besides the thiocyanates some authors presume the existence of a bactericidal substance not yet indentified which would be the product of the living gastric mucosa. This substance would explain that sometimes sterile gastric juice can be detected in spite of the anacidity.

SEEBER (1929) found no difference as to the bacteriologic finding between symptomless anacid persons and those who suffered from diarrhoea or gastric complaints. Accordingly gastrogenous diarrhoea would not depend on the bacterial flora of the stomach. HCl administration — even in large doses — exerts only a temporary inhibition on the growth of the bacteria and thus is not suitable for therapeutical purposes.

Gastric coli positivity is a frequent finding in pernicious anaemia. The bacteriological finding is not influenced by liver therapy (FRANZ and PENDEL 1954). It was observed long ago that a remission may ensue following the sterilisation of the stomach and of the upper part of the small intestine (SEYDERHELM 1924). LICHTMANN et al. (1950) succeeded in normalizing the haematologic status of pernicious anaemia patients by giving antibiotics together with minimal doses of B_{12}. GÄNSSLEN (1953) described that a complete haematologic remission was achieved in pernicious anaemia patients after Supronal administration. The characteristic reticulocyte response could not be observed but there was a long-lasting, steady but moderate increase of the reticulocytes. If the gastric coli infection was not eliminated by Supronal, there was no simultaneous haematologic remission either.

It is similarly known that bact. coli strains are capable of consuming or splitting vitamine B_{12}. This vitamine B_{12} consumption is considerably reduced or ceases entirely if intrinsic factor is given together with B_{12} (HOFF-JÖRGENSEN 1952). FRANZ and PENDL (1954) maintain that without gastric coli infection even patients lacking the intrinsic factor may achieve haematologic remission after the administration of moderate doses of per os B_{12}, because there are no bacteria to destroy the vitamine. This would mean that resorption of the vitamine does occur even without the intrinsic factor which seems only to protect the B_{12} from the destructive action of the bact. coli; in the absence of gastric coli the perorally given B_{12} is also effective. FRANZ and BRANDIS (1953) after having demonstrated the presence of gastric coli infection in a great number of their lymphoid leukaemia patients are of the opinion that some cases of leukaemic anaemia result — at least to a certain extent — of the bacterial destruction of vitamine B_{12}.

The problem of gastric bacterial infection was thoroughly investigated by LEVANTO (1954). In only one out of his 45 pernicious anaemia patients was bact. coli not detectable in the gastric juice. In other achlorhydrias the rate of gastric coli infection was much lower; a relatively high incidence was detected in gastric carcinoma and chronic nephritis cases accompanied by acid deficiency. There was a parallelism between the intensity of coli infection and the gastric pH values; high pH values were accompanied by abundant coli flora. The relation, however, is not an exclusive one; even alkaline gastric juices were encountered without coli population. He succeeded in eliminating the coli infection with the aid of diluted HCl dosage (100 drops three times daily); sometimes a considerable time elapsed between the cessation of the HCl therapy and the reappearance of coli strains. He could not demonstrate any serological and biochemical difference between the coli strains of achlorhydric persons with and without pernicious anaemia. Similarly perniciosus anaemia patients did not seem to represent a special group as to the B_{12}-binding capacity of their coli strains. He concludes that gastric coli positivity is of importance in the assessment of the diagnosis of pernicious anaemia; the absence of the bacteria speaks against the diagnosis. The nature of the interrelation between gastric coli and the haematologic abnormality is unknown, but he does not think that acid deficiency alone would be the decisive factor.

Our own investigations

Bacteriological investigations were carried out in 75 achlorhydric (130 examinations), 18 subacid (acid secretion after 1 mg of histamine) and 40 normacid subjects.

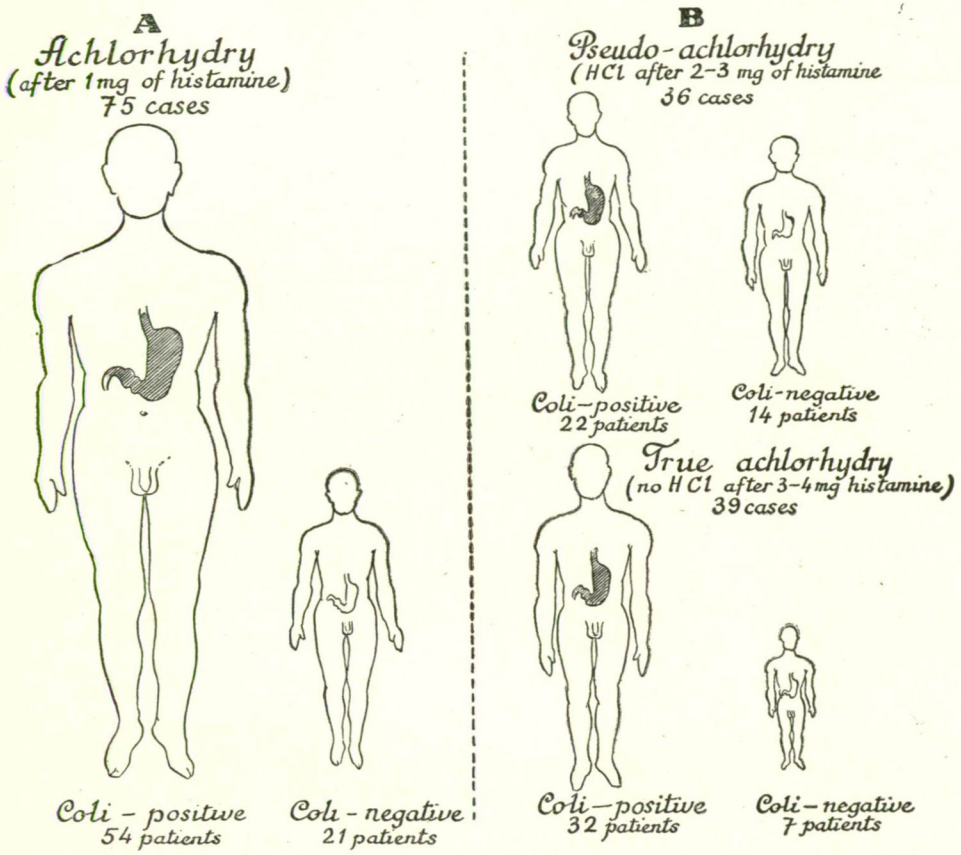
The cause of the discrepancy between the data of various authors dealing with the bacteriology of the stomach may partly be explained by the fact that they used various culture media. Naturally they could not come to the same conclusions. In our work the main emphasis was laid on the demonstration of the coli strains and on the relation of the non-coli population of the stomach to the pharyngeal flora. For technical details we refer to the chapter dealing with methodical problems (page 13).

Bact. coli was found in 54 achlorhydric gastric juices, 4 gastric contents were sterile, the remaining contained pharyngeal flora. In the sterile cases repeated examinations yielded pharyngeal flora in three patients. We want to emphasize that in all 4 cases the augmented histamine test resulted in acid secretion. (Figure 13A)

In the 39 „true achlorhydric" cases (with no acid production after large doses of histamine) 32 had coli, 7 pharyngeal flora in the gastric juice (Figure 13 B).

Figure 13.

The frequency of bact. coli population in the gastric juice of achlorhydrics.



Analysing the true achlorhydric cases with pharyngeal flora it can be stated that in four of them the neutral red solution injected together with the histamine made its appearence in the gastric juice. In a previous chapter (page 38) we tried to demonstrate that the appearence of the acid form of the dye in the gastric juice proves that some HCl production did occur even if the tiny quantity of the secreted acid was not yet demonstrable. Thus using strict criteria these four persons cannot be considered truly achlorhydric. In the other three cases neither acid nor neutral red appeared in the gastric juice, even after 3 mg of histamine. It should be noted that all seven patients with pharyngeal flora in the gastric juice had positive acid instillation tests after parenteral neutral red administration. In our experience (see page 43) the positivity of this test excludes the possibility of a complete gastric mucosal atrophy.

An interesting observation could be made in one of our patients who did not produce acid after 1—2—3 mg of histamine but the neutral red appeared and repeated bacteriological examinations revealed the presence of a pharyngeal flora. After 4 mg of histamine a tiny quantity of HCl could be detected.

There were 20 anaemia perniciosa patients in the group of the „true achlorhydrics"; 19 of them had bact. coli in the gastric juice. In the remaining case repeated examinations showed pharyngeal flora not only in the stomach but in the bile and the jejunal juice as well.

Table 13.

Bacteriological findings in subacid patients.

№	Name		Bacteriological finding				Remarks
			coli	coli + pharyngeal fl.	pharyngeal fl.	sterile	
1.	L. S.	♀	—	+		—	Diabetes mellitus Acidity: 16 – 28
2.	H. L.	♀	—	—	+	—	Acidity: not titrable
3.	J. B.	♂	—	—	+	—	Acidity: 16 – 18
4.	E. F.	♂	—	—	+	—	Acidity: not titrable
5.	Gy. B.	♂	—	—	+	—	Acidity: 17 – 24
6.	M. N.	♀	—	—	—	+	—
7.	L. T.	♂	—	—	—	+	Acidity: 46 – 58
8.	J. K.	♂	—	—	—	+	—
9.	J. J.	♀	—	—	—	+	Acidity: 60 – 64
10.	J. F.	♀	—	—	—	+	Acidity: 30 – 38
11.	P. T.	♀	—	—	+	—	—
12.	E. B.	♀	—	—	+	—	Acidity: 13 – 38
13.	Á. L.	♀	—	—	—	+	Acidity: 24 – 38
14.	R. J.	♀	—	—	+	—	—
15.	J. P.	♀	—	—	—	+	Acidity: 25 – 38
16.	J. H.	♀	—	—	—	+	Acidity: 52 – 102
17.	G. V.	♂	—	—	+	—	Acidity: 38 – 40
18.	G. P.	♀	—	—	+	—	Acidity: 28 – 32

In this latter patient detailed haemotologic analysis left no doubt about his disease being a true Addison—Biermer anaemia: he had megaloblastic bone marrow, macrocytic anaemia (RBC: 1.4 million, Hgb: 1.4 g%, haematocrit: 17%, MCV: 140 μ^3), signs suggesting funicular myelosis. After B_{12} therapy he had reticulocyte response and the RBC began to increase intensively.

In the subacid group the gastric juices were sterile in 8 patients, 9 had pharyngeal flora and one had bact. coli. Reviewing the acidity values of these patients one may find a certain correlation between the degree of acidity and the bacteriological finding. The higher are the acidity values after histamine, the greater is in general the possibility of a sterile gastric juice (Table 13).

Gastric juices of normacid persons were sterile.

We performed bacteriological investigations of the bile in 27 achlorhydric persons whose gastric juice was infected with coli; in all cases the same organisms were found in the bile too. We must emphasize that neither clinical nor laboratory signs of biliary tract infection could be demonstrated in these cases. Achlorhydric persons with pharyngeal flora in the gastric juice contained generally the same bacteria in the bile and even in the jejunal juice.

The above qualitative examinations clearly showed that in our coli positive achlorhydric cases also the duodenal and jejunal juices contained the same bacteria. We performed, therefore, — lacking corresponding comparative literary data — counts of the living bacteria hoping to be able to find out thereby the starting point of the bacterial growth. Samples taken from various parts of the upper gastrointestinal tract showed a bacterial titre of about log 4-8/ml. (Figure 14).

It can be seen that in all three juices examined the average number of living bacteria is of a million order and their fluctuations are not beyond the limit of error.

On the basis of experiments of LEVANTO (1954) cited above we have tried to destroy the gastric coli population of 5 achlorhydric persons with the aid of relatively heavy doses of HCl (3×100 drops of acid. hydrochl. dil. pro die). The patients received the HCl before every meal for 3-5 days. Control examinations performed on the fourth or sixth days showed the unchanged presence of the gastric coli.

To demonstrate a correlation between intragastric pH changes and the bacterial growth we instilled into the stomach a HCl solution of pH 1.5 resp. 2.0 and controlled the bacterial count during instillation and at various moments after it (6 cases).

If recurrent regurgitations do not allow the acid instillation to lower the pH of the gastric contents, no substantial decrease ensues in the bacterial count (Figure 15 A). If the HCl solution is capable, however, to acidify the gastric juice for a shorter (Figure 15 B) or longer (Figure 15 C) period, a simultaneous rapid decrease or total disappearence of the gastric bacterial flora follows. It is important to note, however, that shortly after stopping the HCl instillation, parallely with the rise of the pH values, the number of living coli bacteria returns to the original value.

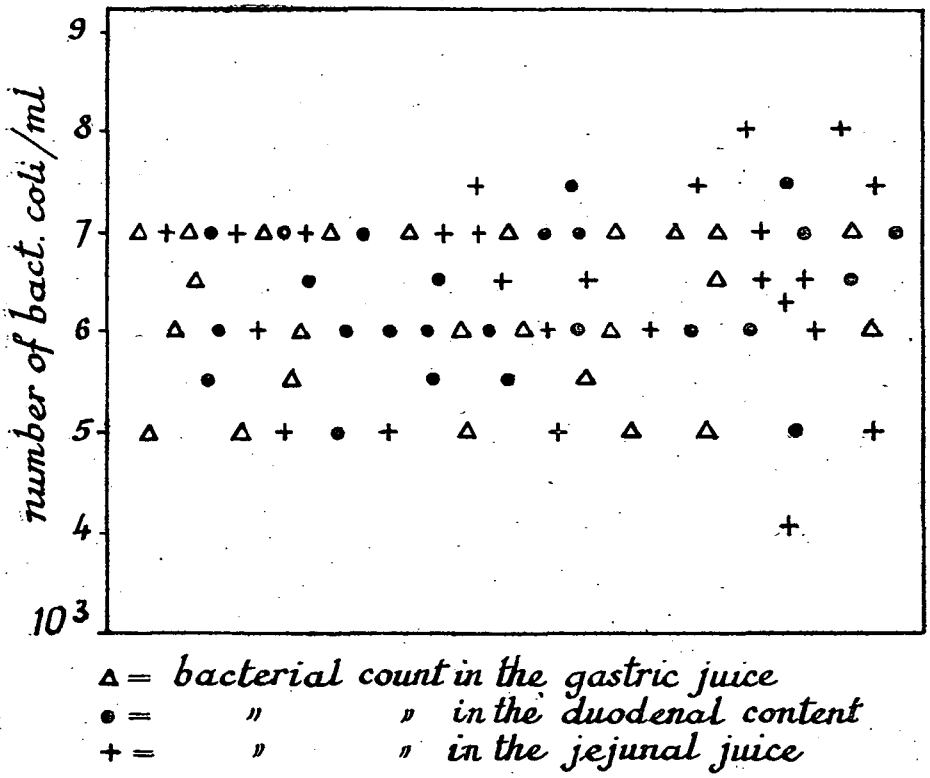
Finally it should be mentioned that we could not detect any relation between the gastric bacteriological finding and the digestive symptoms (e. g. diarrhoea) of our achlorhydric patients.

Discussion

1. *The achlorhydric stomach is rarely if ever sterile. In the smaller part of the cases only pharyngeal flora can be found,* the origin of which is in all probability the saliva swallowed. Thus bacteria may reach the stomach where they are not

Figure 14.

Number of living bact. coli in the gastric, duodenal and jejunal juices of achlorhydric patients.



destroyed because of the lack of gastric HCl and even get into the bile and the jenunal juice. They have no pathologic significance, but may probably cause some diagnostical difficulty (suspicion of liver or biliary tract infection).

In about ²/₃ of our achlorhydric cases coli could be demonstrated in the gastric juice. The rate of coli positivity was higher than the literary standard which in our view can be explained by the fact that stricter than usual criteria were employed for the diagnosis of achlorhydry. If we separate out of the achlorhydric group those persons who did not secrete HCl even after large doses of histamine, the frequency of coli positive finding is further increased. This experience speaks in favour of a positive correlation between the frequency of gastric coli infection and the degree of the acid deficiency. This assumption is further supported by the fact that in all but one pernicious anaemia patients did we find bact. coli in the gastric juice.

Table 14.

The effect on intragastric pH conditions of the diluted hydrochloric acid administered during meal

P. G. ♀

Time	pH
13,45	4,62
13,50 lunch (bouillon, meat with rice) + 100 drops of dil. HCl	
14,00	5,00
14,05	4,62
14,10	3,95
14,15	4,15
14,20	4,35
14,25	4,15
14,30	4,50
15,00	4,62
16,00	4,50
17,00	4,25
18,00	3,25
18,30	6,55
19,00	7,05
20,70	7,15

S.S.K. ♂

12,30	5,87
13,15 lunch (rice soup, meat with potatoes) + 100 drops of dil HCl	
13,30	4,15
13,45	2,45
14,00	3,92
14,15	5,15

J. K ♀

13,00	7,20
14.00 lunch (bouillon, chicken with carrots) + 100 drops of dil HCl	
14,15	6,07
14,30	5,65
14,45	6,38
15.00	6,30

P. G. ♂

Time	pH
19,00	7,45
19,30 dinner (eggs, 50g of cheese, coffee, bread) + 100 drops of dil. HCl	
19,35	5,30
19,45	6,10
19,55	6,30
20,30	6,60

S. F. ♂

12,30	5,30
13,15 lunch (rice soup, veal with potatoes) + 100 drops of dil. HCl	
13,30	3,47
13,32	2,90
13,45	4,62
14,00	5,20
14,15	5,00

Gy. P. ♀

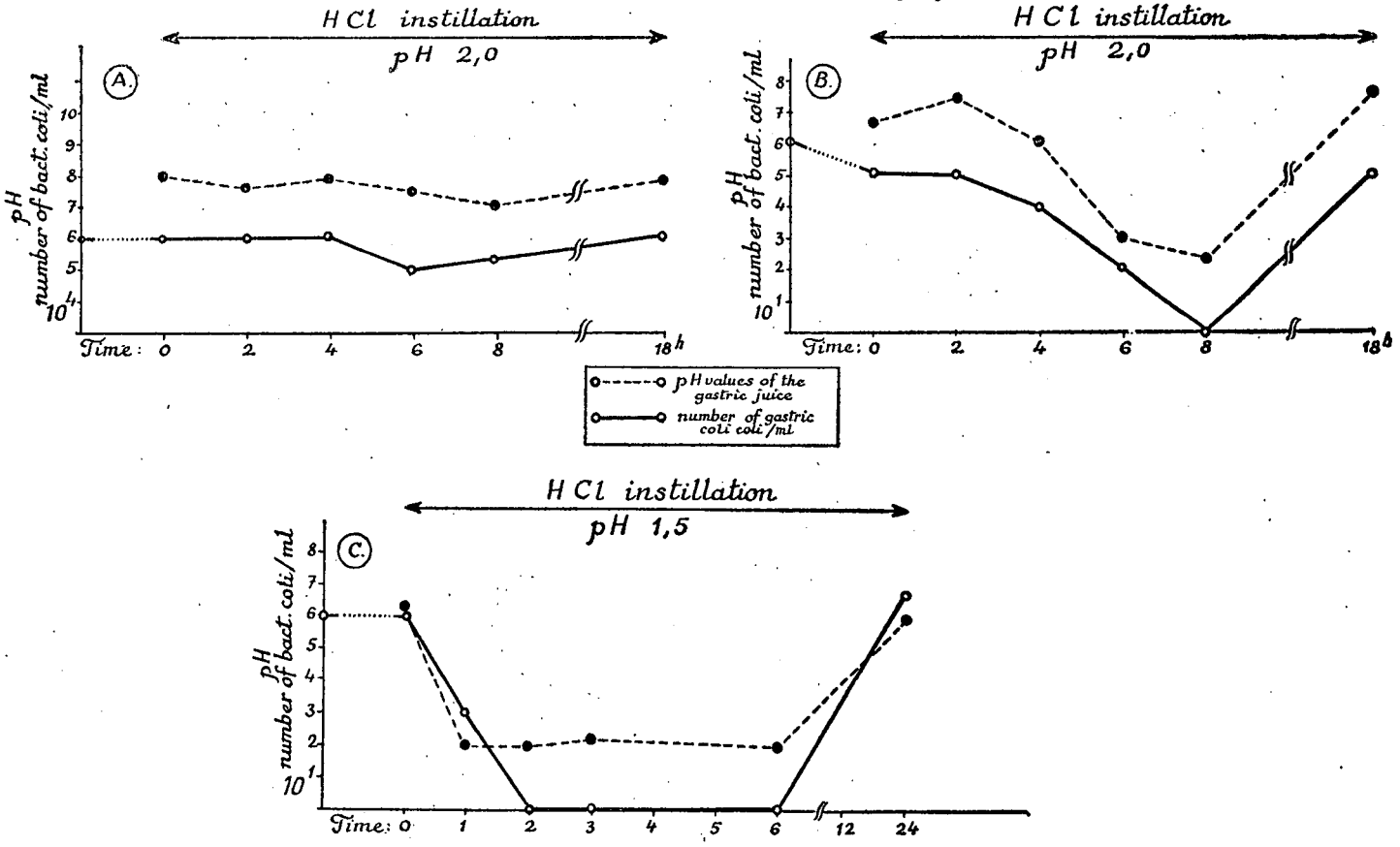
13,30 lunch (rice soup, veal with carrots) + 100 drops of dil. HCl	
13,40	6,1
13,45	6,4
13,50	7,0
13,55	6,9
14,00	6,9

The pharyngeal flora may be detected in subacid gastric juices too, provided that the acidity is constantly low. The effect of a certain concentration of HCl for a certain period seems to be necessary for destroying the bacteria. Generally they rapidly disappear from gastric juices of high acidity. *Gastric juices of healthy normacid people are always sterile.*

2. In our pernicious anaemia patients we repeatedly examined not only the gastric juices but the duodenal and jejunal contents as well and bact. coli could be demonstrated in both latter juices as well. On the basis of our investigations we could not decide the question whether there exists some connection between the coli infection and the B_{12} utilisation. By all means the bacteriologic investigation of the gastric juice may furnish valuable diagnostical help in all cases where the simple or augmented histamine test could not be performed. The lack of gastric coli infection speaks strongly against a pernicious anaemia diagnosis, although it does not exclude the possibility absolutely.

Figure 15.

Intragastric pH changes caused by acid instillation and subsequent quantitative alterations of the gastric coli population.



3. We want to emphasize especially that in our achlorhydric material we could not find any correlation between the bacteriologic finding of the upper gastrointestinal tract and the gastrointestinal symptoms (mainly diarrhoeas). We cannot exclude the possibility that in certain cases the bact. coli population present cannot be classed among the pathogenic factors of the inflammatory lesions of this area, but it is quite sure that many persons are entirely symptomless in spite of their repeatedly verified gastric coli infection. The number of the living bacteria found in these juices does not give any information in this respect. In the bile of a coli cholangitis patient with normacidity or in the urine of a coli-cystitis patient the same coli count was namely found as in the gastric or duodenal contents of a symptomless achlorhydric subject. Anyhow it is most surprising that a given region of the human organism which otherwise is not accustomed to the constant presence of active bacterial colonies and where the most important phase of digestion and absorption takes place, should tolerate without any manifest pathologic alteration the growth of an abundant, biologically active bacterial population.

4. Some practical importance may be contributed to the fact that in cases of coli positive gastric juices the same bacteria could always be found in the duodenal and jejunal contents as well. In cases where the „acid-barriere" is lost, the upper part of the digestive system seems often to contain coli organisms without signs of a florid infection. That is why we think it necessary that gastric analysis should always be performed if the duodenal intubation yields the result of coli positivity in persons without signs of a biliary infection. In cases of achlorhydries it is most useful to perform gastric bacteriologic investigations. The coli positivity in the gastric juice would explain the same finding in the duodenal contents, both being the result of the acid deficiency. In 6 symptomless patients the suspicion of an achlorhydry arose when the duodenal intubation furnished evidence of a coli population without signs of an inflammation; the gastric aspiration gave an achlorhydric gastric juice with an abundant coli content.

5. The coli infection of the achlorhydric subjects happens in all probability through the per os way. We are of the opinion that the bacteria reach the stomach through the mouth on account of an auto- (rarely hetero) infection. They are not destroyed because of the acid deficiency and so settle down in the upper part of the gastrointestinal tract.

XV. THERAPEUTIC PROBLEMS

Achlorhydry may accompany various pathological processes, thus it may be considered as a diagnostical sign in several diseases. Our therapeutical standpoint is a logical consequence of this statement. It is not the achlorhydry itself but the pathological process initiating or sustaining it which has to be influenced through our therapy. Frequently the acid deficiency is only a rest-symptom of some passed off and already quiescent pathological process. The latter occurs in totally symptomless persons and at the (sometimes accidental) discovery of the achlorhydry, the original cause generally cannot be ascertained. In about half of our achlorhydric patients did we find such a symptomless acid deficiency of unknown origin (see page 62). *In our view these achlorhydries do not need any treatment.*

The majority of pernicious anaemia patients serve as good examples for these symptomless achlorhydries. We could not detect any acid production in them; in spite of this during adequate B_{12} treatment they had good appetite and gained weight without any suplementary acid dosage. Generally they had no digestive complaints whatsoever and until their attention was not directed to the acid deficiency, they did not need any gastric therapy.

As to the HCl therapy of anacidity VINOGRADOV et al. (1925) state that canine gastric juice, heavy doses of HCl and pancreatic extract seem to normalise the utilisation of proteins and fats in man. Indeed they administered relatively big doses of HCl (3×45 drops of acid. hydrochl. dil.). BERGMANN (1933) recommended the HCl solution not for substitution but as a soft drink. The maintenance of a weak acidic milieu would be important but this can be achieved by giving sour wine or lemonade as well. BECKER (1934) calculated the daily HCl output of the stomach to be 2,800 mg, he prescribes, therefore, 37,3 ml of acid. hydrochl. *non* dil. to 300 ml of water, the patient has to put 3 table-spoonfuls of it into 1 lit. of water. This 1 lit. of water should be consumed in such a manner that three-quarters should be drunk during the meal, one-quarter after it. Besides he gives 1 g of pepsin to each meal.

KOEHLER and WINDSOR (1943) performed examinations to establish how much HCl is needed for creating optimal milieu for the peptic digestion. To produce a gastric pH surrounding of 1,6-1,8 about 100 ml of normal HCl is needed. MERTEN (1951) maintains that a routine dose of 20 drops of dil. HCl can lower the pH of even 1 lit. of water only to 2.85; added to 1 lit. of mashed potatoes or floursoup even threefold quantity cannot lower the pH but to 5, and also the 6-8 fold quantity only to 3,5. Even for the creation of a catheptic milieu 60-100 drops of dil. HCl would be needed; optimal pH conditions for the peptic activity cannot practically be produced at all. As 20 drops of dil. HCl correspond to 18 ml of 0.2 N HCl, to

reach a pH value of 1,8 during an ordinary meal a minimum of 600 ml would be needed depending on the nature of the food eaten.

DOMINICI and FURBETTA (1953) reported their experience that 100 ml of 1 per cent HCl is capable of producing acidic gastric milieu only for a short period in achlorhydric subjects. They emphasize that HCl administration does not represent a real substitution of the acidic gastric juice; the effect seems to be only the consequence of suggestion.

In six achlorhydric patients we performed examinations to decide how large doses of HCl (3×100 drops of acid. hydrochl. dil.) influence the gastric pH conditions during a meal. Results are shown in Table 14.

Two hours after the HCl administered together with the food or on a fasting stomach the intragastric pH values varied between 5,15 and 7,45. Similar findings were reported by VARTIO and VIRTAINEN (1958) as well.

The sub- or afermentia observed together with the acid deficiency represents a special problem. JUNG et al. (1952) attach great importance to the substitution therapy in cases of enzyme deficiency. In their view acid and enzyme deficiency cause widespread functional disturbances of the gastrointestinal tract which involve changes in the motility, secretion, bacterial flora and nitrogen loss. These changes are abolished „with a single stroke" by the administration of acid and enzyme. This therapy seems especially important during a secretory depression caused by long-standing starvation; e. g. in some parts of Europe after World War II (JUNG et al. 1951). The same authors observed a certain divergence of the acid and enzyme production. They never found isolated pepsin deficiency, so they consider an enzyme therapy never to be indicated in normacid people. This statement is in total accordance with our findings cited before (see page 52). MERTEN (1951) emphasized that a real substitution of gastric enzyme and HCl would need such quantities as are seldom used in medical practice. So in case of a total afermentia in order to achieve normal proteolysis during a normal meal the patient would need ferment preparations containing the enzyme quantity corresponding to that of 100 ml of normacid gastric juice.

Two conclusions may be drawn from the data cited above. First that performing HCl-enzyme substitution we cannot create but the catheptic pH optimum, secondly that a manyfold quantity of the usual HCl dose must be given to reach even that milieu. Generally the digestion of achlorhydric persons approaches without any substitution that of normal people even in cases of insufficient gastric enzyme production because the abundant trypsin regurgitation results in a normal proteolysis (BRAMSTEDT 1953). That is why in most achlorhdyric cases there is no need for enzyme substitution.

It is an old clinical experience that sometimes patients are encountered who after small doses of HCl render account of considerable subjective relief. CROHN (1927) maintains that „whether or not HCl is able to create an acid milieu", its usefulness is beyond doubt. He states that the rapid (?) emptying of the stomach slackens, the pyloric reflex becomes more intensive and the diarrhoea ceases.

To explain the good effect of small doses of HCl several factors may be mentioned:

a) *psychic influence.* The substitution of the gastric acid by the aid of HCl drops seems a logical consequence of the pathological finding even to laymen. Besides the physicians themselves emphasize that the HCl therapy has the purpose of serving as a substitute for the lacking gastric acid. All the changes of a suggestion are thus given and this may entirely explain the alleviation of the neurotic complaints. Even in anacid patients to whom the HCl therapy brought a sub-

jective relief, one can never be sure that this good effect was really caused by the acid supplementation. One can achieve the best results with the HCl therapy in cases of gastric complaints which are highly suspicious to be of neurotic origin. Thus we have experienced a striking good effect in a patient who turned out to be normacid on subsequent gastric analysis.

The simultaneous appearence of neurotic complaints and gastric acid deficiency occurs frequently and so there is ample possibility for spectacular amelioration. BRUMMER (1947) administered to 30 dyspeptic persons on consecutive days the following four medicines in a glass of water: strychnin, sodium bicarbonate, HCl and common salt. 3 patients could not give an answer, 11 benefited of the strychnin, 10 of the bicarbonate; HCl brought relief to only 6 of them. No one seemed to like the salty water. This experiment clearly shows the psychogenic influence of the taste-effect.

The findings of SWYNNERTON and TANNER (1954) are also interesting in this respect. Controlling their achorhydric (no histamine-test were performed) patients with gastroscopically diagnosed atrophic gastritis they discovered that only few of them took the HCl drops ordered, the majority consumed alkaline powders and were mostly satisfied with the effect. Neither did the achlorhydric patients of RAPPAPORT (1955) take the HCl because their symptoms remained unchanged. Sometimes a beneficial effect was observed initially which disappeared, however, after continued therapy. When experiencing gastric pains, these patients, too, took alkalies which brought temporary relief.

b) *influence on gastric emptying and motility.* As early as 1907 CANNON emphasized that gastric HCl plays a decisive role in the regulation of the pyloric activity. On the basis of this theory the rapid gastric emptying of anacid subjects was accepted as a fact by the medical profession especially by radiologists.

Contrary to Cannon's above statement MCCLURE et al. (1920), BRINCK and WICHELS (1933), BECKER (1934) and BRUMMER and BUNDUL (1951) were of the opinion that there is no interrelation between the anacidity and the gastric emptying. Neither did the intestinal passage show any abnormalities (KATILA 1950). With the aid of menthylene blue BRUMMER (1947) succeeded in demonstrating that after the consumption of water or diluted HCl there was no difference in the gastric emptying of anacid persons.

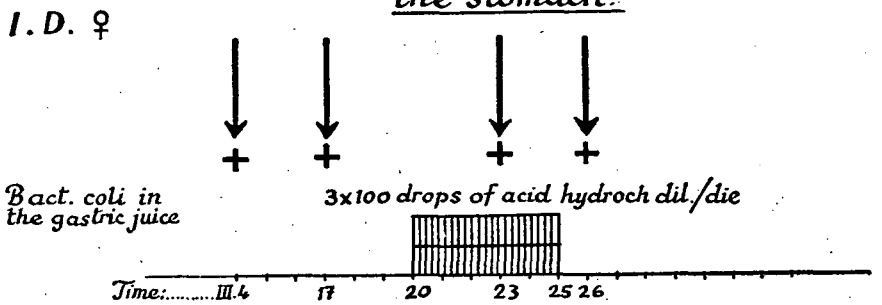
On the basis of literary data cited above we are of the opinion that the effect of diluted HCl cannot be explained by changes in gastric motility.

c) *bactericidal effect.* Scarcely any changes are evoked in gastric pH conditions by the administration of small quantitities of diluted HCl, thus no important alterations may be expected to occur in the gastric bacterial flora. KOEHLER and WINDSOR (1943) emphasize that treatment with diluted HCl does not destroy the gastric bacteria. GOTTSCHLICH (1928) administered large doses of the acid (200 ml of 0.57—0.23% HCl) but could observe changes in the duodenal and jejunal pH only for a short period.

In a previous chapter we reported our experience that we were not able to find any correlation between the gastric flora and the digestive complaints of the patienst examined (see page 101). Neither could we discover any changes in the bacterial flora during and after per os HCl therapy. The findings in one of our patients are shown in Figure 16.

Figure 16.

The effect of HCl therapy (3x100 drops of diluted HCl pro die) on the bact. coli population of the stomach.



Summing up we may say that *small doses of diluted HCl exert sometimes a subjective beneficial effect, the mechanism of which is not yet clarified. Psychic factors seem to play the decisive role.*

As to other therapeutical measures of anacidity we may mention that MOGENA et al. (1932) reported good results after long-term histamine administration. The RBC count increased, the diarrhoea ceased, the patients had better appetite and gained weight. GERÉB and KÖRÖSY (1934) described the good effect of Optacid, a buffer mixture containing Na_2HPO_4 and $NaHSO_4$, which caused the gastric contents to remain between the pH values of 2,6—3,2. DOMINICI and FURBETTA (1953) prescribed to anacid persons a soft diet and administered gastric mucosal extracts, vegetable proteolytic enzymes and lactic acid.

GRUNERT (1953) recommends the use of organic acids for creating an optimal milieu for the catheptic activity. NEUGEBAUER (1954) reported having seen a good effect of such preparations in gastrectomised patients. SHARP and HAZLET (1954) claim that a preparation containing betaine-HCl and pepsin (Normacid) is capable of creating a long-lasting acidic milieu in the stomach; theoretical considerations do not seem to support this assumption.

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Felelős kiadó
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Sajtó alá rendezte
Pálfy Gyula

*

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